# Clinical Trial Protocol

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| | **Document Number:** | **c11253289-04** |
| **EudraCT No.:**<br>**EU Trial No:** | 2016-004572-21 | |
| **BI Trial No.:** | 1368.10 | |
| **BI Investigational Product(s):** | BI 655130 | |
| **Title:** | Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy | |
| **Lay Title:** | A study in patients with mild or moderate ulcerative colitis who take a TNF inhibitor. The study investigates whether bowel inflammation improves when patients take BI 655130 in addition to their current therapy. | |
| **Clinical Phase:** | IIa | |
| **Trial Clinical Monitor:** | [redacted]<br>Phone:<br>Fax: | |
| **Coordinating Investigator:** | [redacted]<br>Phone: | |
| **Status:** | Final Protocol **(Revised Protocol (based on global amendment 3))** | |
| **Version and Date:** | **4.0** | **Date: 04 Mar 2019** |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
|---|---|---|---|
| **Name of company:** | | **Boehringer Ingelheim** | |
| **Name of finished product:** | | N/A | |
| **Name of active ingredient:** | | BI 655130 | |
| **Protocol date:**<br>14 Feb 2017 | **Trial number:**<br>1368.10 | | **Revision date:**<br>**04 Mar 2019** |

| | |
|---|---|
| **Title of trial:** | Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy |
| **Coordinating Investigator** | [redacted]<br>Phone: [redacted] |
| **Trial site(s):** | Multi-centre, multi-national |
| **Clinical phase:** | IIa |
| **Objective(s):** | Safety and efficacy (proof-of concept) of BI 655130 add-on treatment to achieve mucosal healing in patients with mild-to-moderately active ulcerative colitis on TNF inhibitor therapy |
| **Methodology:** | Randomised, parallel-group, placebo-controlled, double-blind |
| **No. of patients:** | |
| **total entered:** | Approximately 30 patients |

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| **each treatment:** | 20 patients BI 655130, 10 patients placebo |
| **Diagnosis :** | Patients with mild-to-moderately active ulcerative colitis on TNF inhibitor therapy |
| **Main criteria for inclusion:** | 1. 18-75 years at screening (at Visit 1 and 2)<br>2. Body weight ≤120 kg (at Visit 1 and 2)<br>3. Diagnosis of ulcerative colitis ≥5 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report<br>4. Currently receiving TNFi treatment with either:<br>- infliximab (INF) with doses (i.e. dose and dosing interval) unchanged for ≥4 months prior to randomisation and detectable drug trough level in blood, OR<br>- adalimumab or golimumab with doses (i.e. dose and dosing interval) unchanged for ≥2 months prior to randomisation and detectable drug trough level in blood.<br>(Patients may or may not have received up to 2 different prior TNFi treatments.)<br>5. Mild or moderate disease activity, defined as:<br>Total Mayo Score (MCS) (≤10), with<br>- modified endoscopic subscore (mESS) ≥2, AND<br>- disease extending 5 cm or more from anal verge<br>6. If patients receive concurrent UC treatments, these need to be on stable doses as below: |

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| | - Oral 5-ASA compounds, provided that dose has been stable for the 4 weeks prior to screening, and/or<br>- Oral corticosteroids (≤10 mg per day of prednisone or equivalent), provided that dose has been stable for the 4 weeks prior to screening, and/or<br>- Azathioprine, 6-mercaptopurin or methotrexate, provided that dose has been stable for the 8 weeks prior to screening.<br>- Probiotics (e.g. S. boulardii) provided that dose has been stable for the 2 weeks prior to screening<br>- Antidiarrheals (e.g. loperamide, diphenoxylate with atropine) for control of chronic diarrhea<br>7. Patients with extensive colitis of >10 years duration or family history of colorectal cancer or personal history of increased colorectal cancer risk must have had an negative colorectal cancer screening within <1 year prior to screening (otherwise to be done during screening colonoscopy). |
| **Test product(s):** | BI 655130 |
| **dose:** | 1200 mg at Weeks 0, 4 and 8 |
| **mode of administration:** | i.v. |
| **Comparator products:** | Placebo |
| **dose:** | Placebo at Weeks 0, 4 and 8 |

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| **mode of administration:** | i.v. |
| **Duration of treatment:** | 12 weeks |
| **Endpoints** | Primary endpoint:<br>• Mucosal healing (MCS mESS ≤1) at Week 12<br><br>Secondary endpoints:<br>• Treatment emerging adverse events<br>• Clinical remission based on Mayo score (total MCS ≤2 points, and all subscores ≤1 point) at Week 12<br>• Histological remission (Robarts (RHI) score ≤6) at Week 12 |
| **Safety criteria:** | Physical examination, vital signs, 12-lead ECG, laboratory tests, adverse events, serious adverse events and tolerability. The intensity grading of AEs and abnormal laboratory values will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0. |
| **Statistical methods:** | The evaluation of endoscopic activity at Week 12 is the primary objective in this trial and is described using the proportion of patients with mucosal healing at this time-point.<br><br>Randomisation will be stratified based on concomitant use (yes, no) of infliximab. The unadjusted absolute risk difference versus placebo will be calculated simply as the difference in the observed proportion of responses between BI 655130 and placebo, for the FAS. A 95% Newcombe confidence interval around this difference will be provided. The influence of the stratification variable on the |

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| | primary endpoint will be characterized in exploratory analyses.<br>Safety will be summarized descriptively. | | |

# FLOW CHART

| **Trial periods** | **Screening** | | **Treatment** | | | | | **Follow-up** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **V1a[1]** | **V1b[1]** | **V2[2]** | **V3** | **V4** | **V5** | **EOT** | **FU1** | **FU2** | **FU3** | **EOS** |
| **Week** | **-5 to -1** | **-4 to -1** | **0** | **2** | **4** | **8** | **12** | **16** | **22** | **28** | **36** |
| **Day** | **-35 to -8** | **- 28 to -6** | **1** | **15** | **29** | **57** | **85** | **113** | **155** | **197** | **253** |
| **Visit window (days)** | **N.A.** | **N.A.** | **0** | **±2** | **±3** | **±3** | **±4** | **±4** | **±4** | **±4** | **±4** |
| **Informed consent** | X | | | | | | | | | | |
| In-/exclusion criteria | X | X | X | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Smoking/alcohol | X | | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Prior therapies | X | | | | | | | | | | |
| Ulcerative colitis history | X | | | | | | | | | | |
| Sigmoidoscopy or colonoscopy + biopsy[3,4] | | X | | | | | | | | | |
| Sigmoidoscopy + biopsy[4,5] | | | | | | X | X | | | | |
| Physical exam (incl. vital signs)[6] | $X^C$ | $X^T$ | $X^T$ | $X^T$ | $X^T$ | $X^C$ | $X^C$ | $X^T$ | $X^T$ | $X^T$ | $X^C$ |
| Weight | X | | X | | X | X | X | | | | X |
| Height | X | | | | | | | | | | |
| 12-lead ECG | X | | X | | X | X | X | | | | X |
| Pregnancy test[7] | X | | X | | X | X | X | X | X | X | X |
| Concomitant therapy | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X |
| Total Mayo score[8] | | X | | | | X | X | | | | |
| Partial Mayo score[8] | | X | X | X | X | X | X | X | X | X | X |

| **Trial periods** | **Screening** | | **Treatment** | | | | | **Follow-up** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **V1a**[1] | **V1b**[1] | **V2**[2] | **V3** | **V4** | **V5** | **EOT** | **FU1** | **FU2** | **FU3** | **EOS** |
| **Week** | **-5 to -1** | **-4 to -1** | **0** | **2** | **4** | **8** | **12** | **16** | **22** | **28** | **36** |
| **Day** | **-35 to -8** | **- 28 to -6** | **1** | **15** | **29** | **57** | **85** | **113** | **155** | **197** | **253** |
| **Visit window (days)** | **N.A.** | **N.A.** | **0** | **±2** | **±3** | **±3** | **±4** | **±4** | **±4** | **±4** | **±4** |
| Safety laboratory tests[9] | X | | X | X | X | X | X | X | X | X | X |
| HBV-DNA monitoring[9] | | | X | | | | X | | | | |
| Infections screening (Hep B, Hep C, HIV) | X | | | | | | | | | | |
| QuantiFERON-TB test | X | | | | | | | | | | |
| Blood sampling for TNFi level[10] | X[10] | X[10] | | | | | X[10] | | | | |
| Blood sampling for PK[11] | | | X | X | X | X | X | X | X | X | X |
| Blood sampling for ADAs[11] | | | X | | X | X | X | X | X | X | X |
| Blood sampling for biomarkers[11] | | | X | X | | X | X | | | | X |
| Blood sampling for immune cell | | | X | | | X | X | | | | |
| Blood sampling for gene expression | | | X | | | X | X | | | | |
| Optional blood sampling for DNA banking | | | X | | | | | | | | |
| Stool sampling for biomarkers | X[12] | X[12] | X | X | X | X | X | X | X | X | X |
| Stool sampling for enteric pathogens | X[12] | X[12] | | | | | | | | | |
| IBDQ[13] | | | X | | | X | X | | | | X |
| EQ-5D(-5L)[13] | | | X | | | X | X | | | | X |
| Diary dispensing[14] | X | | | | | | | | | | |
| Diary review | | X | X | X | X | X | X | X | X | X | X |
| Study drug administration | | | X[2,15] | | X[15] | X[15] | | | | | |
| Study completion | | | | | | | | | | | X |

**Footnotes:**

1. Visit 1b should be at least 1 day after Visit 1a.
2. First study drug administration will be administered during mid-cycle of background TNFi dosing.
3. In general, a flexible sigmoidoscopy will be performed during screening period. A full colonoscopy must only be done, if a colonoscopy has not been done in past 3 years in order to assess disease extent and (if applicable per local guidelines) to exclude cancer.
4. Two sets of mucosal biopsies will be taken; 1 set for gene expression analyses and 1 set for histopathology/IHC analyses at each visit indicated. At visits with study drug administration this should to be done prior to the study drug infusion. Colonoscopy and sigmoidoscopy images will be centrally read by an external independent assessor(s); management of images will be performed by an external vendor.
5. Sigmoidoscopies will be performed at Week 8 and Week 12. A sigmoidoscopy must be performed if a flare of UC occurs during follow up period. This can be performed within an extra un-scheduled visit.
6. Physical examination: C=complete, T=targeted. Refer to Section 5.3.1. In addition, at Visits 2, 4 and 5 vital signs will be assessed at approximately 5 and 120 minutes after end of study drug administration. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after all doses of study drug.
7. Only applicable for women of childbearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flow Chart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result.
8. Total Mayo score includes endoscopy. Partial Mayo score excludes endoscopy.
9. Includes clinical chemistry, haematology, coagulation and urinalysis assessments. At visits with study drug administration safety laboratory tests and HBV (hepatitis B virus)-DNA monitoring should to be done prior to the study drug infusion.
10. TNFi trough level will be done during screening period (V1a or V1b, or at a unscheduled visit) under consideration of the individual dosing schedule of the respective TNFi; if screening Visit 1a does not occur ≤24 hours before the next *scheduled* TNFi application, Visit 1b should be timed accordingly to allow endoscopy and TNFi trough level to be performed at the same visit; eligibility will be determined based on the real trough level collected at maximum 1 day before the next scheduled TNFi application. TNFi drug level will be done at EOT visit. Only if possible, this should be done as a trough level.
11. At study visits with study drug administration, pre-dose PK/ADA and biomarkers/flow cytometry samples and gene expression samples will be obtained within 2 hours prior to start of i.v. infusion.
12. Stool sampling will be done during screening period (V1a or V1b, or at an unscheduled visit).
13. Inflammatory Bowel Disease Questionnaire (IBDQ) and EQ-5D(-5L), a questionnaire developed by EuroQoL group, must be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments and, if possible, before any interaction with the investigator or other members of the study team. Refer to Section 6.2
14. A diary will be used by the patient for the daily reporting of bowel movement frequency and rectal bleeding (blood in stool). This information will be used for the calculation of Mayo score at the visits as indicated in the Flow Chart. In addition, background medication will be recorded by patients in diary provided and assessed by study staff. Refer to Section 6.2.1.
15. Patients who terminate study drug early should be encouraged to follow all study procedures per the Flow Chart until at least Week 12, but not receive any more study drug at the respective visits. These patients do have the option to do EOS visit earlier, i.e. 20 weeks after last study drug administration. Until then they should follow the Flow Chart. Patients refusing to return to the study site should at least provide safety information and the MCS subscores by phone at the respective visits.

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| AMP | Auxiliary Medicinal Product |
| ALT | Alanine Aminotransferase |
| 5-ASA | 5-aminosalicylic acid |
| AST | Aspartate Aminotransferase |
| AUC | Area under the Curve |
| BI | Boehringer Ingelheim |
| BMS | BioMarker Set |
| CA | Competent Authority |
| CD | Crohn's disease |
| Cmax | Maximal Concentration |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CRS | Cytokine Release Syndrome |
| CRO | Contract Research Organisation |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DILI | Drug Induced Liver Injury |
| DNA | Deoxyribonucleic Acid |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| ELISA | Enzyme Linked Immunosorbent Assay |
| EMA | European Medicines Agency |
| EOS | End of Study |
| EOT | End of Treatment |
| eCRF | Electronic Case Report Form |
| eDC | Electronic Data Capture |
| ePRO | Electronic Patient Reported Outcome |
| EQ-5D(-5L) | Questionnaire developed by EuroQoL Group |
| EudraCT | European Clinical Trials Database |
| FAS | Full Analysis Set |
| FCP | Faecal Calprotectin |
| FcR | Fc Receptor |
| FDA | Food and Drug Administration |
| FIH | First in Human |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GPP | Generalized Pustular Psoriasis |
| Hep | Hepatitis |
| HIV | Human Immunodeficiency Virus |

| | |
|---|---|
| IB | Investigator's Brochure |
| IBD | Inflammatory Bowel Disease |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon gamma |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IHC | Immunohistochemistry |
| i.m. | intramuscular |
| IL-36R | Interleukin-36 Receptor |
| INF | Infliximab |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISF | Investigator Site File |
| ITE | Indirect Target Engagement |
| ITT | Intention-To-Treat |
| i.v. | intravenous |
| kDa | Kilodalton |
| LPDD | Last Patient Drug Discontinuation |
| MCID | Minimal Clinically Important Difference |
| MCS | Mayo Score |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| mESS | Modified endoscopic subscore |
| MMRM | Mixed Model Repeated Measures |
| MoA | Mode of Action |
| N | Number |
| NCE | New chemical entity |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NIMP | Non-Investigational Medicinal Product |
| NRI | No Response Imputation |
| OPU | Operative Unit |
| PBMC | Peripheral blood mononuclear cells |
| PBO | Placebo |
| PCR | Polymerase Chain Reaction |
| PD | Pharmacodynamics |
| PGA | Physician Global Assessment |
| PK | Pharmacokinetics |
| p.o. | per os (oral) |
| PoCC | Proof of Clinical Concept |
| PPP | Palmoplantar Psoriasis |
| PPS | Per Protocol Set |
| PRO | Patient Reported Outcome |
| q.d. | quaque die (once a day) |
| RBS | Rectal Bleeding Subscore |
| RCTC | Rheumatology Common Toxicity Criteria |

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|---|---|
| REML | Restricted Maximum Likehood |
| REP | Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present |
| RHI | Robarts Histopathology Index |
| RNA | Ribonucleic Acid |
| qw | Weekly (once a week) |
| SAE | Serious Adverse Event |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| s.c. | Subcutaneous |
| SFS | Stool Frequency Score |
| SOP | Standard Operation Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TB | Tuberculosis |
| TCM | Trial Clinical Monitor |
| TGF-ß | Transforming Growth Factor beta |
| t.i.d. | ter in die (3 times a day) |
| TNF | Tumor necrosis factor |
| TNFi | Tumor necrosis factor inhibitor |
| TSAP | Trial Statistical Analysis Plan |
| UC | Ulcerative Colitis |
| ULN | Upper Limit of Normal |
| V | Visit |
| VAS | Visual Analog Scale |
| VEGF | Vascular Endothelial Growth Factor |
| w | Week |
| WBC | White Blood Count |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

Ulcerative Colitis (UC) has an estimated incidence of 24.3 and 19.2 cases per 100,000 persons per year in Europe and the USA, respectively, resulting in a continuously rising prevalence [R15-0886]. UC is characterized clinically by abdominal pain, fever, and blood or mucosa-containing diarrhea, and pathologically by inflammatory lesions in the gastrointestinal mucosa. Inflammatory lesions characteristically occur distal to the terminal ileum, and by confinement of lesions to the mucosa and submucosa without transmural inflammation. UC typically follows a relapsing and remitting course, and is associated with substantial acute and long-term morbidity and increased mortality. The mainstays of drug therapy for UC are: orally administered aminosalicylates, glucocorticoids, oral immunomodulatory agents azathioprine and 6-mercaptopurine, and TNFinhibitors (TNFi). In patients with mild UC, 5-ASAs are safe and effective for induction and maintenance treatment. Glucocorticoids, immunomodulators, TNFi , and more recently vedolizumab, are reserved for patients with moderate to severe disease, in whom the primary goals of drug therapy are to induce and subsequently to maintain remission from signs and symptoms of active disease.

Current biologic treatment of UC is associated with approximately one third of patients each failing with primary or secondary non-response. In addition, treatment may be limited due to safety and tolerability issues. Therefore, despite of therapeutic progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared to the current therapeutic standard.

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody blocking IL-36α, IL-36β and IL-36γ binding to IL-36R. The IL-36 pathway has been associated with the pathogenesis of several inflammatory diseases including inflammatory bowel diseases, pustular psoriasis and psoriasis vulgaris. Emerging preclinical data suggest that IL-36R is a potential target for the treatment of inflammatory bowel diseases, such as ulcerative colitis.

## 1.2 DRUG PROFILE

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL-36R signaling. Binding of BI 655130 to IL-36R is anticipated to prevent the subsequent activation of IL-36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

*Preclinical studies*

BI 655130 binds to human IL-36R with high binding avidity. BI 655130 effectively inhibits IL-36 ligand-stimulated NF-κB activation, IL-8 release and IFN-γ secretion in human cell cultures or PBMC stimulated with IL-36α, IL-36β, or IL-36γ combined with IL-12.

Mutations BI 655130`s Fc receptor were introduced to abrogate FcR binding activity and function. Direct assessment of the impact of these mutations in the IgG1 FcR binding sites revealed that the mutations abrogate both antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector functions and indicate that BI 655130 will be a non-depleting therapy in vivo.

*Toxicology studies*

BI 655130 does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI 655130. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI 655130 stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.

These preclinical data suggest BI 655130 can be safely administered to humans for up to 13 weeks.

*Clinical PK/PD studies*

BI 655130 or placebo (PBO) was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight (1368.1). Safety and tolerability of all tested i.v. doses was good. There were no drug-related SAEs. AEs categorized as related to treatment were observed in 3/19 (15.8%) subjects in the placebo group and in 7/59 (11.9%) subjects treated with BI 655130. The most frequent treatment-emergent AEs were nasopharyngitis (BI 655130: 21%; PBO: 15%), headache (BI 655130: 9%; PBO: 15%), influenza like illness (BI 655130: 7%; PBO: 10%), and diarrhoea (BI 655130: 3%; PBO: 10%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose. There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12 lead ECGs, vital signs, and cardio-monitoring.

PK analysis showed that exposure ($AUC_{0\text{-tz and Cmax}}$) to BI 655130 seems to increase with increasing dose in a greater than dose-proportional manner from 0.01 to 0.3 mg/kg while exposure increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition kinetics for BI 655130. The saturation of the non-linear elimination pathway is likely occurring after 0.3 mg/kg and BI 655130 seems to exhibit linear kinetics from the next dose-level onwards. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. However, caution should be taken in interpreting the ADA results because the drug concentrations in many ADA samples exceeded the drug tolerance level of the ADA assay (100 µg/mL). Pharmacodynamic effects in this FIH Single Rising Dose trial (c03320877) were assessed by indirect target engagement (ITE) of IL-36R by BI 655130 using an ex-vivo whole blood stimulation assay. Preliminary analyses indicate that >94% peripheral IL-36R receptor occupancy is achieved with doses ≥3 mg/kg from 30 minutes post infusion to 10 week.

In the multiple rising dose trial (1368.2), BI 655130 or placebo have been administered to healthy male volunteers at multiple ascending i.v. doses of 3, 6 and 10 mg/kg given qw for 4 weeks (i.e. 4 administrations), as well as a single dose cohort of 20 mg/kg. All dose groups (8 patients each, 3:1 on active or PBO) have completed dosing and 4 weeks of follow-up. Overall, BI 655130 was well tolerated. There were no AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader.

Based on population pharmacokinetic modelling informed by both studies, the exposures of BI 655130 in this trial 1368.10 are not predicted to exceed the exposures tested and found safe with the highest tested dose regimen in 1368.2 (20 mg/kg qw for 4 weeks). Specifically, body weight was included as a covariate in the PK model which accounted for a small portion of inter-individual variability in exposure. This model was then used to simulate with variability the pharmacokinetic profile for a typical 30 kg individual dosed 1200 mg every 4 weeks and compared to a 60 kg individual receiving 20 mg/kg weekly as shown in the plot below:

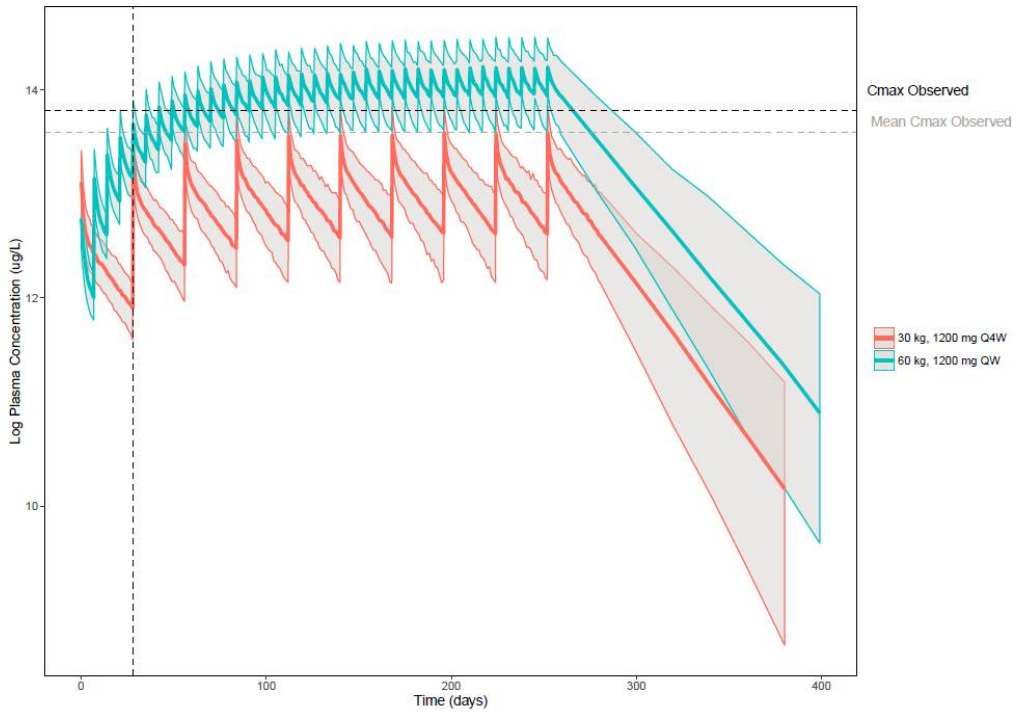


Figure 1.2.1: Population pharmacokinetic modelling comparing the 1200 mg q4w dosing regimens of a 30 kg individual in 1368.10 to the 1200 mg qw dosing regimen of a 60 kg subject in 1368.2.

The shaded region in the plot represents the 90 % prediction/confidence interval of the simulated PK profiles for the respective dosing regimens. As can be seen from the plot, the 30 kg predictions do not exceed the maximum observed $C_{max}$ from the 1368.2 trial for the planned 1368.10 trial duration. Additionally, the AUC and $C_{max}$ predicted at steady state for the 30 kg individual do not exceed the steady state exposures predicted after weekly dosing of 20 mg/kg. Assuming no differences in drug clearance between healthy volunteers and patients with UC, for patients with a body weight of 30 kg, the median AUC at steady state is predicted to be 2.88 fold lower (35,595 ug/mL*day vs 12,344 ug/mL*day) in the 30 kg subject dosed 1200 mg q 4 weeks compared to the 20 mg/kg dosing regimen given weekly. Similarly, the median $C_{max}$ (log transformed) at steady state is predicted to be lower at 13.58 ug/L (13.4 – 13.9 (90% CI)) for the 30 kg individual compared to 14.3 ug/L (13.98 – 14.53 (90% CI)).

*Summary*
BI 655130 is an anti IL-36R antibody with a high potential to block IL-36R signaling. BI 655130 has been tested in healthy volunteers with single and multiple doses up to 20 mg/kg i.v. (single dose) or 20 mg/kg (multiple doses), which were all safe and well tolerated. In addition, IL-36R inhibition shows a favorable nonclinical safety profile. Therefore, BI 655130 might be a promising drug to treat patients suffering from ulcerative colitis.

For more detailed description of the BI 655130 profile please refer to the current Investigator`s Brochure" (c03320877).

# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is currently under development for the treatment of ulcerative colitis (UC). Its unique dual modes of action includes anti-inflammatory effects as well as tissue remodeling effects and thus may provide a clear advantage over current drugs and investigational compounds, which target inflammatory pathways only. The potential BI 655130 effects on remodeling may turn into increased mucosal healing and reduced stricturing and fistulizing complications of IBD.

The link between IL-36R driven inflammation and epithelial inflammation has led to the hypothesis that IL-36R signalling may play an important role in inflammatory bowel diseases such as UC:

- IL-36R and its ligands are expressed in intestinal biopsies from patients with chronic IBD;
- IL-36-induced genes are upregulated in human intestinal myofibroblasts and correlate with gene signatures observed in ulcerative colitis and Crohn's disease (CD) patients;
- Human IL-36 ligands in cell culture enhance epithelial intestinal barrier permeability, a hallmark of IBD pathogenesis;
- IL-36R signalling induces in human intestinal myofibroblasts and macrophages not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF-β, matrix metalloproteinase), which differentiates this mechanism from TNF alpha and IL-23 pathways;
- IL-36R signalling in disease relevant cells such as intestinal myofibroblasts and macrophages induce not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF-β, matrix metalloproteinase)
- An antagonist anti-mouse IL-36R antibody ameliorates intestinal inflammation in various acute and chronic murine colitis models.

While these findings support a prominent role of IL-36R in driving intestinal inflammation, in vitro studies have demonstrated synergy of IL-36 and TNF in inducing pro-inflammatory cytokine stimulation and disease activity markers such as calprotectin. In addition, IL-36 regulated genes have been found upregulated in UC patients non-responsive to infliximab. These findings suggest a synergistic role of both cytokines in the pathogenesis of ulcerative colitis and provide a scientific rationale for inhibiting both, TNFi and IL-36 simultaneously in patients with UC.

Therefore, it is hypothesized that in patients with mild or moderate UC but persisting endoscopic activity on treatment with TNFi, a quite frequent outcome of TNFi treatment in patients with initially moderate or severe UC, short-term add-on treatment with the IL-36 inhibitor BI 655130 may induce mucosal healing, which may be maintained by continued treatment with the TNFi after withdrawing the IL-36 inhibitor BI 655130. This concept will be tested in the present trial.

In addition, data on clinical effect, safety and pharmacokinetics of 12 weeks of BI 655130 treatment in UC patients will be gained and compared to the BI 655130 exposure achieved with equivalent doses in healthy volunteers. These data will help understand the PK characteristics of BI 655130 in UC, which may differ from those in healthy volunteers and patients with other diseases due to the expected intestinal protein loss subsequent to mucosal inflammation and ulceration in the colon.

These findings will support planning and conduct of later stage proof-of-concept, dose-finding and pivotal trials.

The most recent and more detailed information is available in the current IB (c03320877).

## 2.2 TRIAL OBJECTIVES

The objectives of this trial are safety and efficacy (proof-of-concept) of induction of mucosal healing by BI 655130 add-on therapy in patients with mild or moderate ulcerative colitis and persisting endoscopic activity despite pre-existing TNFi treatment.

This trial will explore safety and efficacy of a dose of BI 655130 that was modelled to achieve the similar exposures as the highest exposures tested and found safe and tolerable in preceding single and multiple dose studies in healthy subjects, as add-on to pre-existing TNFi treatment. Secondary and further objectives include assessment of the pharmacokinetic (PK) profile of BI 655130 and early exploration of specific biomarkers with potential usefulness to predict clinical efficacy or safety outcome or help understand BI 655130`s mode of action.

## 2.3 BENEFIT - RISK ASSESSMENT

**Potential Benefits**

Preclinical profiles of BI 655130 and clinical data from healthy volunteer trials suggest that BI 655130 is safe and may address an unmet medical need in UC patients by a dual anti-inflammatory and anti-fibrotic mechanism of action (cf. Section 2.1). In-vitro studies have demonstrated synergistic effects of IL-36 and TNF in inducing pro-inflammatory responses. Thus, combined inhibition of both cytokines may act synergistically to induce deep and durable remission in UC patients (cf. section 1.2, and IB (c03320877)). The requirement of stable TNFi dosing and detectable blood levels will ensure proper TNFi dosing.

- An individual benefit may arise for patients who achieve mucosal healing. Persistent endoscopic activity is associated with rectal bleeding and other symptom compromising patient`s quality of life (R16-4637), while its absence is associated with improved clinical outcomes (reductions in immunosuppressive treatments, hospitalisations, colectomy and colorectal cancer (R16-0572). In this study, the combination treatment aims to *induce* mucosal healing, while continued treatment with the partially effective TNFi aims to *maintain* mucosal healing. For patients relapsing after BI 655130 termination, approved drugs are available as rescue treatment, including TNFi or the integrin inhibitor vedolizumab.

- Under the assumption of a positive exposure/response relationship, the highest safe and tolerable dose schedule is expected to provide the best chance to induce remissions and achieve a positive proof-of-clinical-concept (PoCC). If the study achieves a positive PoCC, this study will be followed up by detailed phase II exploration of various lower dose levels.

- In case of a study outcome demonstrating insufficient clinical activity in presence of adequate drug exposure (comparable to exposures effective in other indications), the evaluation of pathway engagement and disease modification genes and biomarkers will guide additional studies of BI 655130 in other patient populations with UC or CD. Thus, apart from potentially providing a benefit to individual patients, participation in this study may contribute to generate a group benefit for this or other patient populations.

**Potential Risks**

As with any immune modulating agent, BI 655130 has the theoretical potential to impair immune function resulting in an increased risk of infection or lymphoma. In line with IL-36 being a member of the pro-inflammatory IL-1 cytokine family, IL-36 has been shown in vitro to stimulate various pro-inflammatory cytokines and activate NFκB. The potential to impair immune function may be increased by combining this compound with a TNFi. However, BI 655130 has been tested and found safe in healthy volunteer studies, and the risk of combining it with TNFi will be mitigated by thorough safety measures.

- No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (IB (c03320877), Section 5.1.2).

- The clinical safety and tolerability profile of BI 655130 has been tested and found favourable in male healthy subjects treated with i.v. multiple doses up to 20 mg/kg body weight once weekly for weeks: BI 655130 was safe and well tolerated in both completed phase I trials at all dose groups with no reporting of any dose dependent, severe or serious AE (for details cf. section 1.2 and IB c03320877). In addition, further phase I studies in healthy volunteers (1368.3, 1368.9) and clinical proof-of-concept studies are ongoing in different indications (1368.11 – GPP; 1368.15 – PPP; 1368.4 – UC; 1368.10 - UC) under regular surveillance by an independent DMC. None of these studies has so far generated any specific safety signal (see IB c03320877). In summary, as of September 2017, more

than 170 subjects have been exposed to active drug without a dose limiting safety or tolerability issue.

Importantly, based on population pharmacokinetic modelling informed by1368.1 and 1368.2, the exposures of BI 655130 in this trial are predicted to not exceed the exposures tested and found safe with the highest tested dose regimen in 1368.2 even in subjects with a body weight as low as 30 kg (see section 1.2). As can be seen from the plot in figure 1.2.1, the predictions for a 30 kg individual do not exceed the maximum observed $C_{max}$ from the 1368.2 trial for the planned 1368.10 trial duration. However, the expected difference in drug clearance between healthy volunteers and patients with UC will further increase the differences in exposures between 1368.2 and 1368.10 and thus increase the safety margin. On the other hand an increased body weight might have negative impact on the compound`s efficacy. However, such an effect will be limited based on the minor impact of body weight on PK variability, and the fact that the 1200 mg dose corresponds to a dose of ≥10 mg/kg for patients <120 kg, where any dose of ≥3 mg/kg has provided maximum indirect target engagement and biological activity in healthy subjects (cf. section 1.2). Therefore, there is no need to limit enrolment to certain body weights.

- Thus, the exposure range expected with the selected dose regimen in study participants will be covered by safety data from healthy volunteer studies even if the subject weighed as low as 30 kg. However, these predictions are made based upon comparable exposures between healthy volunteers and IBD patients, while in fact lower systemic exposures are typically found in UC patients compared to healthy subjects due to higher drug clearance of monoclonal antibodies resulting from:
    - intestinal protein loss caused by exudative enteropathy (R16-5741; R16-5706)
    - higher degree of systemic inflammatory burden (R13-3046)
    - higher expression of the target molecule (IL-36R) in diseased tissues as compared to peripheral blood of healthy subjects, which may increase the effect of target-mediated drug disposition on clearance of BI 655130
- Such lower exposure found with many biologics in IBD patients represents the basis for requiring higher doses in IBD compared to other indications (e.g. infliximab, adalimumab, ustekinumab) (R13-5226; R15-4915; R16-0692; R16-0573).
- In contrast to new chemical entities, the safety and tolerability profile of biologics is generally driven by the downstream effects of target molecule binding, and is not directly dose dependent at exposures approaching full receptor occupancy, which has been achieved for BI 655130 in the healthy volunteer trials. The only exception might be infusion reactions, which have not been reported in phase I and will be closely monitored as AE of special interest (AESI).
- The safety risk of the TNFi combination will be mitigated by the pre-selection of patients who respond to and tolerate their current TNFi. Moreover, production of IL-1b, a key cytokine in native and adaptive immune response, is stimulated through many other

signals beyond IL-36R activation, which will remain intact. However, as a worst case scenario of IL-1b inhibition, a previous clinical trial has assessed the triple combination of the IL-1R inhibitor anakinra (approved for Rheumatoid Arthritis (R16-4481), with the TNFi ethanercept and methotrexate. Though this study demonstrated an increased risk of serious infections (7.4% vs 0% on placebo/methotrexate), such treatment was considered manageable and there were no fatalities (R16-4413). In contrast, the physiological relevance of the in-vitro finding of *partial* IL-1b inhibition following IL-36 inhibition is unclear.

- Patients randomised to placebo will not be exposed to undue risks, since they will continue to receive the standard of care for patients with such mild or moderate disease, a situation where the TNFi is usually continued without modification until the patient relapses.

- Finally, the theoretical risk of profound immunosuppression will be mitigated by thorough safety measures: (i) exclusion of patients with history or increased risk of malignancies or infections; (ii) close clinical monitoring for AEs, including Rheumatology Common Toxicity Criteria (RCTC) criteria for intensity grading as project standard and the definition of lymphomas, opportunistic or severe infections as adverse events of special interest (AESI), allowing accelerated investigation and reporting; (iii) selection of sites experienced in treatment of IBD patients with biologics; and (iv) implementation of an independent data-monitoring committee (DMC).

Other risks are those related to blood sampling and intravenous infusion of study medication. Colonoscopy or sigmoidoscopy with biopsy, although generally well tolerated, can be associated with complications. Therefore, endoscopies will in most patients be limited to flexible sigmoidoscopies, which do not require complete bowel preparation and are safer and better tolerated. A screening colonoscopy will only be required if a colonoscopy has not been done in past 3 years in order to assess disease extent or to exclude cancer if applicable in accordance with local guidelines (P14-15417). The investigation of endoscopic endpoints is requested by FDA and EMA as key part of efficacy assessment. The number of three sigmoidoscopies per patient (up to a maximum of four sigmoidoscopies or one colonoscopy plus three sigmoidoscopies in patients requiring colonoscopy and experiencing a flare) over a 36 week time frame is acceptable to patients, considering that the safety risks are limited, investigators are highly experienced and that UC patients are usually familiar with the burden and risks of endoscopies from their own disease history. The risks are outweighed by the benefit of developing a new drug in this severe disease.

Due to its antagonistic effect it is considered highly unlikely that BI 655130 may lead to a clinical cytokine release syndrome. In addition, preclinical and clinical phase I evaluation did not suggest cytokine release induced by BI 655130. However, occurrence of such a syndrome will be carefully monitored for as an AESI.

Manifestations of local and systemic hypersensitivity reactions are readily detectable, transient in nature, and in general manageable with standard medical treatment. Specific safety measures will be taken during the trial. Following the i.v. infusion, the patients will be monitored for infusion reactions at the site for two hours after infusion.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also section 5.3.6.1.

**Summary of benefit-risk assessment**

Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of BI 655130 it is considered likely that UC patients will not be exposed to undue risks and adverse events in relation to the information that is expected to be gained from this trial. Considering the medical need of the development of an effective and well tolerated drug for the therapy of UC, the benefit of this trial is considered to outweigh the potential risks for individual UC patients participating in this trial.

The benefit-risk profile is thus considered appropriate for an experimental therapy at this stage of clinical development.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, randomised, parallel-group, multiple-doses, placebo-controlled, double-blind Phase IIa study. Approximately 30 eligible patients with mild to moderate UC and persisting endoscopic activity will be randomised at 2:1 ratio, stratified based on concurrent infliximab use, into treatment arm (approximately 20 patients) versus placebo (approximately 10 patients) shown in Figure 3.1: 1.

Overall treatment duration is 12 weeks with additional 24 weeks follow-up. However, the timing of start of treatment (V2) during mid cycle of the TNFi dosing cycle, and primary endpoint assessment at Week 12 are driven by the notation of spontaneous disease activity fluctuations in patients in TNFi. This will reduce the confounding effect of such fluctuations.

Patients will receive BI 655130/placebo as described in Figure 3.1: 1. The overall dosing schedule will be the same in all treatment arms in order to keep the blind, this is further described in Section 4.1.4. The first dose of study drug will be administered at mid-cycle of background TNFi dosing.

The analysis of the efficacy and safety data collected up to Week 12 will be performed when the last patient completes the Week 12 visit, which will include the primary endpoint. The final analysis of the entire trial data collected through Week 36 will be performed once all patients have completed the last scheduled trial visit.

Individual patient participation is concluded when the patient has completed the last planned visit. The “last-patient-last-visit-primary-endpoint” is the last scheduled primary endpoint visit at Week 12 completed by the last patient. The end of the trial is defined as “last patient out”, i.e. last scheduled visit completed by last patient.

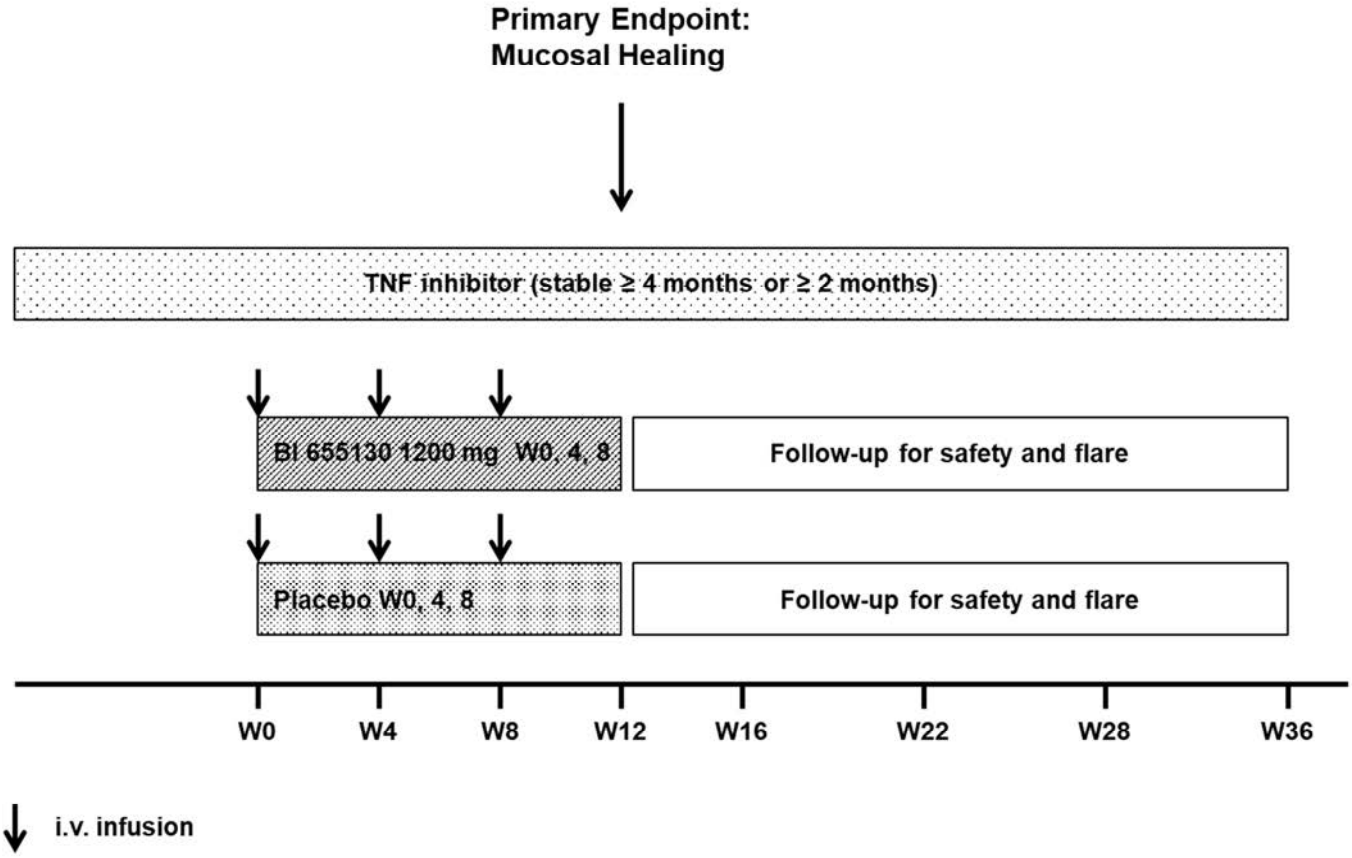


Figure 3.1: 1 Trial design

### 3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at different centres participating in this multi-centre trial. Tasks and responsibilities are defined in a contract.

A project-independent, fully-external data-monitoring committee (DMC), will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial due to safety or ethical concerns. Measures will be put in place to ensure blinding of the project team and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

Relevant documentation on the participating (principal) investigators and other important participants, including their curricula vitae, will be filed in ISF.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF. Central reading of endoscopies and central evaluation of histopathology will be done. Details will be provided in ISF.

## 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A randomised, double-blind and placebo controlled trial was considered most appropriate to demonstrate a first PoCC and safety of BI 655130 as add-on to a TNFi treatment in patients with ulcerative colitis.

The selection of target patients with mild or moderate disease and persistent endoscopic activity during TNFi treatment was based on the high unmet need in such patients, where persistent mucosal inflammation is associated with an increased risk of disease progression, cancer and other complications. This population is rather abundantly available at IBD referral centres and there are no established drugs for this condition, nor are these patients addressed by other clinical trials. Having failed previous TNFi treatments in the past will not confound the mechanistic studies in tissue and blood based on emerging internal biomarker data and will thus be lifted as an exclusion criterion.

The concept of BI 655130 add-on to continued TNFi treatment is based on the expectation of synergistic anti-inflammatory activity and the hypothesis of an additional tissue remodelling activity of BI 655130, which should translate into increased rates of clinical remission including mucosal healing (cf. section 2.1). Also, the continuation of the pre-existing TNFi is expected to maintain remission beyond the duration of BI 655130 treatment. To explore this

effect, the follow-up period will be extended until 24 weeks after the end of treatment, to capture differences in relapse rates between both arms. This extended follow-up period will also enable studies of wash-out PK to enhance the understanding of differences between UC patients and subjects with other diseases, e.g. by intestinal protein losing enteropathy or differences in target mediated drug disposition.

Treatment start (Visit 2, randomisation) has to be scheduled to occur during the mid of the patient`s individual TNFi dosing cycle (i.e. Week 4 after last dose for INF patients, Week 1 after last dose for adalimumab patients, Week 2 after last dose for golimumab patients – to be adapted accordingly if actual TNFi dosing deviates from the standard dosing intervals) to minimize the confounding effect of spontaneous disease fluctuations on the outcome.

The treatment duration of 12 weeks with BI 655130 was selected to cover a longer induction period compared to currently approved biologic treatments and is covered by currently available preclinical GLP toxicology studies. As clinical remissions under induction treatment in active UC are typically detected after 6-8 weeks of treatment with biologics, the duration of 12 weeks will allow to observe mucosal healing and/or clinical remissions, provided BI 655130 is clinically active in UC. It will also determine the kinetics of response and optimal duration of induction treatment. After the end of BI 655130, patients will stay on their TNFi as maintenance therapy and be observed for the occurrence of relapses. In case of disease worsening during BI 655130 treatment or endoscopically confirmed relapse after the end of treatment, patients will receive standard treatment (switch to treatment with a systemic steroid, conventional immune modulator or a different approved TNFi or the integrin inhibitor vedolizumab) under consideration of the patient`s previous treatment history per the investigator`s discretion. Due to exclusion of patients previously exposed to vedolizumab therapy, patients entered in this trial will have a rescue treatment option with this drug. Therefore, a limited combination treatment with BI 655130 of 12 weeks, followed by TNFi maintenance treatment is justified.

The placebo control group is required to explore both the primary efficacy endpoint and the safety profile of BI 655130 add-on in patients with UC on background treatment with TNFi in this yet unstudied patient population. An active comparator for such a treatment situation is neither established nor approved.

Thus, this trial design is considered adequate to achieve the objectives outlined above.

## 3.3 SELECTION OF TRIAL POPULATION

A total of approximately 30 patients will be randomised in this trial. A sufficient number of patients will be screened to meet this randomised goal. Patients will be recruited at approximately 20 sites in multiple countries. The planned number of patients per site is 1 – 2. Recruitment will be competitive.

Women of childbearing potential (WOCBP) with a level of acceptable contraception, in alignment with the Clinical Trials Facilitation Group guideline on “Recommendations related to contraception and pregnancy testing in clinical trials” will be allowed to participate, as

supported by results from pre-clinical toxicology and teratology studies with BI 655130. Please refer to the IB for more details.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

### 3.3.1 Main diagnosis for trial entry

Mild-to-moderately active ulcerative colitis on TNF inhibitor therapy

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

### 3.3.2 Inclusion criteria

1. 18-75 years, males or females (at Visit 1 and 2)
2. Body weight ≤120 kg (at Visit 1 and 2)
3. Diagnosis of ulcerative colitis ≥5 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report
4. Currently receiving TNFi treatment with either:
   - infliximab (INF) with doses (i.e. dose and dosing interval) unchanged for ≥4 months prior to randomisation and detectable drug trough levels in blood, OR
   - adalimumab or golimumab with doses (i.e. dose and dosing interval) unchanged for ≥2 months prior to randomisation and detectable drug trough level in blood.

   (Patients may or may not have received up to 2 different prior TNFi treatments).
5. Mild or moderate disease activity, defined as:

   Total Mayo Score (MCS) (≤10), with
   - modified endoscopic subscore (mESS) ≥2, AND
   - disease extending 5 cm or more from anal verge
6. If patients receive concurrent UC treatments, these need to be on stable doses as below:
   - Oral 5-ASA compounds, provided that dose has been stable for the 4 weeks prior to screening, and/or
   - Oral corticosteroids (≤10 mg per day of prednisone or equivalent), provided that dose has been stable for the 4 weeks prior to screening, and/or
   - Azathioprine, 6-mercaptopurin or methotrexate, provided that dose has been stable for the 8 weeks prior to screening.

- Probiotics (e.g. S. boulardii) provided that dose has been stable for the 2 weeks prior to screening

- Antidiarrheals (e.g. loperamide, diphenoxylate with atropine) for control of chronic diarrhea

7. Patients with extensive colitis of >10 years duration or family history of colorectal cancer or personal history of increased colorectal cancer risk must have had an negative colorectal cancer screening within <1 year prior to screening (otherwise to be done during screening colonoscopy).
8. Women of childbearing potential (WOCBP) must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

   Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

9. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial

### 3.3.3 Exclusion criteria

***Gastrointestinal Exclusion Criteria***

1. Extensive colonic resection, subtotal or total colectomy
2. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
3. Prior use of more than two different TNF inhibitors or vedolizumab
4. Any treatment limiting safety or tolerability issue of the concurrent TNF inhibitor
5. Concurrent treatment with rectal 5-ASA compounds, parenteral or rectal corticosteroids (incl. budesonide) within 2 weeks, any investigational drug within 12 weeks or 5 half-lives, whatever is longer, or any prior dose of natalizumab or rituximab prior to screening
6. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
7. Evidence of infection with C. difficile or other intestinal pathogen <28 days prior to screening
8. Currently require or are anticipated to require surgical intervention for UC
9. Colonic moderate or severe mucosal dysplasia
10. Colonic adenomas (unless properly removed)

11. Primary sclerosing cholangitis
12. Faecal transplant ≤6 months before screening

***Infectious Disease Exclusion Criteria***

13. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), live vaccination within 6 weeks prior to screening, past organ or stem cell transplantation)
14. Active or latent TB (Patients with positive QuantiFERON TB test are excluded. Patients with suspected false positive or undeterminable QuantiFERON TB result may be re-tested)
15. Any severe infection <30 days prior to screening, including chronic or acute hepatitis B or C infection

***General Exclusion Criteria***

16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
17. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned during the study, e.g. hip replacement.
18. Pathological safety lab parameters: haemoglobin <8.5 g/dL, total white blood count (WBC) <3500 cells/µl, neutrophils <1000 cells/µl, thrombocytes <75.000/µl, albumin <30 g/l, creatinine ≥2 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x ULN, total bilirubin >1.5 x ULN (patients with Gilbert's syndrome are not excluded).
19. Currently enrolled in another investigational device or drug study, or less than 12 weeks (or 5 half-lives, whichever is greater) since ending another investigational device or drug study(s), or receiving other investigational treatment(s)
20. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
21. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than ulcerative colitis, surgical procedure, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data

### 3.3.4 Removal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomisation, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and eCRF.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication. Please refer to Section 4.2.2 for restricted medication during this trial.
- If, in the investigator's opinion, the patient requires additional medical therapy or dose increase in patient`s baseline medication to treat the underlying UC due to disease worsening or a flare (cf. section 4.2.1) the study drug must be discontinued, while the patient should be further followed-up in the trial as outlined below.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for the remaining scheduled visits and follow up as outlined in the Flow Chart. Should the patient not agree to continue the remaining trial visits as scheduled after the premature treatment discontinuation, all efforts should be made to bring in the patient to the primary endpoint visit at Week 12, and/or to the End of Residual Effect period at 20 weeks after the last dose of trial medication.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site

2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial

3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

# 4. TREATMENTS

## 4.1 INVESTIGATIONAL TREATMENTS

Multiple doses of BI 655130 and placebo to match BI 655130 will be administered intravenously. All products will be supplied by Boehringer Ingelheim.

### 4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 655130

| | |
|---|---|
| Substance: | BI 655130 |
| Pharmaceutical formulation: | Solution for infusion |
| Source: | Boehringer Ingelheim Pharma GmbH & Co. KG |
| Chemical form: | Anti-human IL-36 Receptor mAb |
| Molecular weight: | 146 kDa |
| Unit strength: | BI 655130 150 mg/vial (20 mg/mL) |
| Route of administration: | Intravenous infusions |
| Posology: | 1200 mg at Week 0, 4 and 8 |
| Duration of use: | 12 weeks |

Table 4.1.1: 2 Description of test product placebo to BI 655130

| | |
|---|---|
| Substance: | Placebo to BI 655130 |
| Pharmaceutical formulation: | Solution for infusion |
| Source: | Boehringer Ingelheim Pharma GmbH & Co. KG |
| Chemical form: | Not applicable |
| Molecular weight: | Not applicable |
| Unit strength: | Not applicable |
| Route of administration: | Intravenous infusions |
| Posology: | Weeks 0, 4 and 8 |
| Duration of use: | 12 weeks |

### 4.1.2 Selection of doses in the trial

The aim of this small exploratory study is to achieve PoCC for a new MoA in UC. Based on other effective anti-cytokine drugs in IBD and pre-clinical assays for IL-36 inhibition, a linear or logistic rather than a bell-shaped dose-response curve is expected. Thus, the highest tolerated dose should provide the highest likelihood to achieve this objective. Whether lower doses will be sufficient to achieve maximum efficacy will be subject of subsequent studies.

The primary endpoint of mucosal healing is well established in the scientific literature (R16-0172), accepted by regulatory agencies (EMA (R17-0441) and FDA (R17-0038) guidances), objective and responsive if read by an independent blinded central reader (R17-0435) and clinically meaningful in that its relevance for long-term clinical outcome of UC is well accepted (R16-0572). Therefore it is suited to demonstrate PoCC for a new compound in a small study.

The fixed rather than weight-based dose regimen of 1200 mg given at Weeks 0, 4 and 8 has been selected for the following reasons:

- Early trials of therapeutic monoclonal antibodies often investigate body weight based regimens to reduce the inter-subject variability in drug exposure. However, there is generally only modest contribution of body weight to overall pharmacokinetic (PK) and pharmacodynamics (PD) variability of monoclonal antibodies. Furthermore, monoclonal antibodies are highly target-specific and offer a relatively large therapeutic window as compared to new chemical entities. Therefore, most monoclonal antibodies are approved at fixed doses in antibody/target excess in order to cover target turnover and maximize efficacy. (R13-4749, R10-6267, R13-4753, R13-4750, R13-4754).

- Body weight has been included in the current PK model as a covariate indicating decreased exposure with increasing body weight. The current model indicates that body weight explains less than 15% of between-subject variability in PK of BI 655130 when comparing a model with and without body-weight as a covariate of exposure.

- A fixed dose regimen will minimize the potential for dosing errors due to less complex dose calculation, study drug preparation and administration as compared with weight based dosing. It will also facilitate dose finding and PK-PD analyses due to covering a wider weight/exposure range (R10-6267).

- This dose regimen is the highest covered by current healthy volunteer PK and safety data irrespective of body weight.

- Currently approved or investigational biologics (e.g. TNFi, vedolizumab, ustekinumab) have established 4-8 weeks duration of induction treatment in UC; a longer induction period of 12 weeks was selected to allow assessment of the response kinetics for BI 655130, which represents a new and clinically non-validated MoA. The dosing interval of once every 4 weeks is supported by the long half-life of BI 655130 of approximately four weeks. The discontinuation of BI 655130 treatment after 12 weeks is supported by preclinical GLP toxicology studies with the surrogate antibody and will allow study of the

PK and PD wash-out profile (clinical effect and biomarker) of BI 655130. It is justified to stop BI 655130 since patients stay on maintenance treatment with their original TNFi.

### 4.1.3 Method of assigning patients to treatment groups

During Visit 2, eligible patients will be randomised to receive treatment in a 2:1 ratio (BI 655130 : placebo) and stratified by concomitant use of infliximab according to a randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

Randomised patients who did not receive study drug due to early discontinuation or due to a skipped visit will be replaced.

Details regarding the use of the IRT are described in the site-user manual available in the ISF.

### 4.1.4 Drug assignment and administration of doses for each patient

In this trial, a dose of 1200 mg of BI 655130 will be administered intravenously at Day 1, Week 4, and Week 8. The concentration of the application solution in the infusion bag will be 20 mg/mL.

Detailed instructions for the preparation of the infusion solution, the volume to be administered and the infusion rate are provided in the ISF.

In case of safety concerns, e.g., due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, interrupting the infusion and - provided no further safety concern exists - restarting at a slower rate. Further, based on his medical judgement he/she will provide medications such as steroids, etc., as needed (cf. section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject and closed with a mandarin.

The administration of the trial medication on all applicable study days will be done under supervision of the investigating physician or a designee at the site. If available, a pharmacist should prepare the study medication. The so-called four eye principle (two-person rule) should be applied for preparation (e.g. choosing the correct vials with the correct medication number) and administration of trial medication. .

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, study drug of the following visit should not be administered within 14 days of the prior dose. There should be at least 14 days between two consecutive study drug administrations.

### 4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients and investigators involved in trial conduct will remain blinded with regard to the randomised treatment assignments until after the final trial database lock. The randomisation code will be kept secret by Clinical Trial Support up to the final database lock. For the primary analysis which is to be performed at Week 12 once all randomised patients have completed the Week 12 visit, the blind status of trial personnel through the remainder of the trial will be clarified in a logistics plan which is to be finalized prior to the unblind for the Week 12 analysis. Please refer to Section 7.4 for further details.

The randomisation codes will be provided to bioanalytics prior to last patient out to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim' s Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and will not be shared further.

Formal treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, and subsequent to database lock for the Week 12 final analysis, as well as subsequent to the final trial database lock. Treatment will be officially unblinded once the final trial database lock has been performed. Procedures to protect the integrity of the trial including the blind of patients, investigators, and study personnel through the final trial database lock will be implemented and are further described in section 7.4.

### 4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The investigational product consists of a carton holding a single vial of the trial medication. The required information according to the Annex 13/EU GMP Guideline is provided on the vial and carton. Each carton will have a unique medication number.

The investigational product will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For examples of the labels, refer to the ISF.

### 4.1.7 Storage conditions

Investigational Medicinal Product (IMP) will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately. Refer to ISF.

Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial patients according to the CTP by authorized personnel as documented in the trial staff list.

### 4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee.
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal investigator

Only authorized personnel as documented in the form ‘Trial Staff List’ may administer medication to trial patients. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. All used and partially used medication must be destroyed locally by the trial site. Receipt, usage and return or disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor, the investigator / pharmacist / investigational drug storage manager must verify that all unused drug supplies have been returned by the clinical trial staff and all used or partially used supplies have been destroyed by the trial site, and that no remaining supplies are in the investigator's possession.

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

If the patient requires additional medical therapy or dose increase of baseline UC medication to treat the underlying UC due to disease worsening or a disease flare (increase in partial MCS score by ≥ 2 points from nadir, confirmed at a second subsequent visit AND by an increase by ≥1 point from nadir in the modified Endoscopic Subscore (mESS)), the study drug must be discontinued and patients may receive other treatment for active disease. Such patients will be considered as treatment failures in the ITT analysis.

If disease activity cannot be treated adequately prior to Week 12 without the use of the medication prohibited by the protocol or changes in the doses of allowed medication (above), the patient must be discontinued from study drug according to Section 6.

Treatment options for identified AE of special interest:

Infusion reactions

- In case of infusion reactions emerging during or after infusion of study drug, the investigator should consider in accordance with severity of the reaction and local standard of care to
    - Immediately interrupt the infusion
    - Treat with systemic anti-histamines and intravenous steroids
- Based on patient`s clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate reactions (according to RCTC grading in ISF) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655130/placebo in the Investigator Site File.

Opportunistic, severe or serious infections, TB infection

- The investigator should discontinue treatment with BI 655130 and consider interruption of the TNFi. Treatment of the infection has to be initiated according to local standard of care.

Lymphoma

- The investigator should discontinue treatment with BI 655130 and consider interruption of the TNFi. Diagnostics and treatment has to be initiated according to local standard of care.

Cytokine release syndrome (CRS)

- This syndrome manifests when a large numbers of immune cells becomes activated and releases inflammatory cytokines. It is clinically characterized by fever, chills, rigor and rash, possibly with nausea, dyspnoea, tachycardia and hypotension.

- Potentially life-threatening complications of a cytokine release syndrome include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. In case of suspicion of a cytokine release syndrome, it is recommended to measure IL-6 levels in the local laboratory if the assay is available.

- The investigator should discontinue treatment with BI 655130 and consider interruption of the TNFi. Aggressive supportive care is essential for patients experiencing CRS, with early intervention for hypotension and treatment of concurrent infections. IL-6 receptor blockade with tocilizumab remains the mainstay pharmacologic therapy for CRS, though indications for administration vary among centers. Corticosteroids should be reserved for neurologic toxicities and CRS not responsive to tocilizumab (R16-5751).

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Any concomitant therapies should be limited to those essential for the non-gastrointestinal care of the patient. All concomitant medications and the reason(s) for use will be documented throughout the course of the study.

Following concomitant UC therapies are allowed to be continued during the study without dose modifications: any dose modification or de-novo initiation of any of these restricted medications will be considered a rescue treatment.

- Oral 5-ASA, stable dose for 4 weeks prior to screening and during study

- Oral corticosteroids (≤10 mg per day of prednisone or equivalent), stable dose for 4 weeks prior to screening and during study

- Azathioprine, 6-mercaptopurin or methotrexate, stable dose for 8 weeks prior to screening and during study
- Probiotics (e.g. S. boulardii), stable dose for 2 weeks prior to screening and during study
- Antidiarrheals (e.g. loperamide, diphenoxylate with atropine) for control of chronic diarrhea; stable doses are encouraged

Restrictions regarding previous and concomitant treatment are summarized in Table 4.2.2.1: 1.

Table 4.2.2.1: 1 Restricted medications

| **Medications or class of medications** | **Restriction duration** |
|---|---|
| Investigational products | 12 weeks or 5 half-lives, whichever is greater, prior to screening and during study |
| Vedolizumab, natalizumab, rituximab, other than current TNFi | Not allowed neither before nor during study |
| Cyclosporine, tacrolimus, mycophenolate mofetile and other immunomodulators | 8 weeks prior to screening or 5 half-lives, whichever is greater, prior to screening and during study |
| 5-ASA compounds | Rectal 5-ASA compounds 2 weeks prior to screening and during study |
| Corticosteroids | Parental (s.c., i.m., or i.v.) or rectal corticosteroids:<br>2 weeks prior to screening and during the study |
| NSAID | Chronic use<br>(Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted.) |
| Live vaccines | 6 weeks prior to screening and during study |
| Antibiotics for IBD | 4 weeks prior to screening and during study |

4.2.2.2 Restrictions regarding women of childbearing potential

Women of childbearing potential and men able to father a child must use the contraception methods described in the patient information.

## 4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol by authorised study personnel (e.g. study nurse). The measured plasma concentrations will provide additional information about compliance.

Any missed dose has to be documented and reported to the CML.

# 5. VARIABLES AND THEIR ASSESSMENT

## 5.1 TRIAL ENDPOINTS

### 5.1.1 Primary Endpoint(s)

- Mucosal healing (MCS mESS ≤1) at Week 12

### 5.1.2 Secondary Endpoint(s)

- Treatment emerging adverse events
- Histological remission (Robarts (RHI) score ≤6) at Week 12
- Clinical remission based on Mayo score (total MCS ≤2 points, and all subscores ≤1 point) at Week 12
- Modified clinical remission based on Mayo score (total modified MCS ≤2 and: RBS =0, SFS =0 or 1 and drop ≥1 from baseline, AND mESS ≤1) at Week 12

## 5.2 ASSESSMENT OF EFFICACY

Mucosal healing will be assessed by endoscopy. Mucosal healing will be defined as a Mayo modified endoscopic appearance subscore ≤1.

The changes in UC activity during the trial will be assessed at visits including endoscopies using the total Mayo score (disease activity score) including the PGA (physician global assessment) and modified ESS (any degree of friability defines a score of at least 2) scores and the Robarts histopathology index (histologic activity score). mESS and Robarts histology index will be read by a central reader. At all visits not including endoscopic assessment, the partial MCS (partial MCS; all subscores except mESS) will be recorded to assess clinical disease activity. Please refer to Appendix 10.2 (Mayo Score/modified Mayo score) and to Appendix 10.3 (Robarts histopathology index) for further details.

## 5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events
- Serious adverse events (SAEs)
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)
- Physical examination
- Vital signs
- 12-lead ECG

### 5.3.1 Physical examination

Complete and target physical examinations will be performed at visits as described in the Flow Chart.

Complete physical examination will include vital sign assessment and general appearance as well as evaluation of all organ systems. Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

### 5.3.2 Vital Signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements. At dosing visits (Visits 2, 4 and 5) vital signs evaluations will be performed pre-dose and additional evaluations will be taken approximately at 5 minutes post-dose and 120 minutes post-dose.

### 5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 and 2 will be performed at the central laboratory service provider. A local laboratory may be used for selected tests in exceptional cases.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in ISF. For time points of laboratory sampling, see Flow Chart.

Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice) of the patients will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

Clinically relevant abnormal findings will be reported as baseline conditions or AE's. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

Table 5.3.3: 1 Exclusionary testing[1]

| Category | Test name |
|---|---|
| Infections screening | Hepatitis B Surface Antigen (qualitative)<br>Hepatitis C Antibodies (qualitative)<br>HIV-1, and HIV-2 Antibody (qualitative) |
| TB screening | [redacted] |
| Serum Pregnancy test (only for female patients of childbearing potential) | Human Serum Chorionic Gonadotropin |
| Drug level | TNFi trough level |
| Stool studies to evaluate for enteric pathogens | Salmonella<br>Shigella<br>Yersinia<br>Campylobacter<br>Vibrio<br>E. coli O157/H7<br>Clostridia difficile toxin<br>Enteric parasites and their ova (including Cryptosporidia) |

[1] At screening only (Visit 1)

Table 5.3.3: 2 Laboratory tests

| Category | Test name |
|---|---|
| Haematology | Haematocrit (Hct)<br>Haemoglobin (Hb)<br>Mean cellular haemoglobin (MCH)<br>Mean cellular haemoglobin concentration (MCHC)<br>Mean cellular volume (MCV)<br>Red Blood Cell Count/ Erythrocytes<br>Reticulocyte Count<br>White Blood Cells / Leukocytes<br>Platelet Count/ Thrombocytes |
| Diff. Automatic | Neutrophils (relative and absolute count)<br>Eosinophils (relative and absolute count)<br>Basophils (relative and absolute count)<br>Monocytes (relative and absolute count)<br>Lymphocytes (relative and absolute count) |
| Diff. Manual (if Diff Automatic is abnormal) | Neutrophils, bands (Stabs)<br>Neutrophils, polymorphonuclear (PMN)<br>Eosinophils<br>Basophils<br>Monocytes<br>Lymphocytes |
| Coagulation | Activated Partial Thromboplastin Time (aPTT)<br>Prothrombin time (INR)<br>Fibrinogen |
| Enzymes | AST (GOT)<br>ALT (GPT)<br>Alkaline Phosphatase (AP)<br>Creatine Kinase (CK)<br>CK-MB, only if CK is elevated<br>Gamma-Glutamyl Transferase (GGT/γ-GT)<br>Lactic Dehydrogenase (LDH)<br>Amylase<br>Lipase |
| Electrolytes | Calcium<br>Sodium<br>Potassium<br>Chloride<br>Bicarbonate |

Table 5.3.3: 2 Laboratory tests (continued)

| Category | Test name |
|---|---|
| Substrates | Glucose<br>BUN (blood urea nitrogen)<br>Uric acid<br>Creatinine<br>eGFR (estimated by CKD-EPI formula) (only at screening)<br>Bilirubin Total<br>Bilirubin Direct (if total is elevated)<br>Bilirubin Indirect (if total is elevated)<br>Troponin (Reflex, in case of elevated CK)<br>Protein, Total<br>Albumin<br>C-Reactive Protein (CRP) (high sensitivity)<br>Cholesterol, total<br>Triglycerides<br>LDL-Cholesterol<br>HDL-Cholesterol<br>Protein electrophoresis (only at screening) |
| Specific gamma-globulin quantification | IgE[1], IgG |
| Urine Pregnancy test (only for female patients of childbearing potential) | Human Chorionic Gonadotropin in urine |
| Serum Pregnancy test (only for female patients of childbearing potential if urine pregnancy test is positive) | Human Serum Chorionic Gonadotropin |
| Hormones (only at screening) | TSH (free T3 and free T4 in case of abnormal TSH result) |
| Urinalysis (dipstick) | Urine Nitrite<br>Urine Protein<br>Urine Glucose<br>Urine Ketone<br>Urobilinogen<br>Urine Bilirubin<br>Urine RBC/ Erythrocytes<br>Urine WBC/ Leukocytes<br>Urine pH |
| Urine-Sediment (microscopic examination, only if urine analysis abnormal) | Urine Sediment Bacteria<br>Urine Cast in Sediment<br>Urine Squamous Epithelial Cells<br>Urine Sed. Crys., Unspecified<br>Urine Sediment RBC/ Erythrocytes<br>Urine Sediment WBC/ Leucocytes |
| Drug level | TNFi drug level (only at EOT visit) |
| HBV (hepatitis B virus)-DNA monitoring | HBV-DNA (quantitative PCR) at baseline (Visit 2) and EOT Visit |

[1]Only in case of allergic reaction

### 5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart.

ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position and will always precede blood sampling. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.

The electronic version, if applicable, or dated and signed printouts of the ECG will be regarded as source data and will be stored in the patient's medical file.

### 5.3.5 Other safety parameters

In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (cf. ISF) and proceed as described in section 4.2. 1. Also draw plasma sample for IgE and ADA (anti-drug antibodies), as detailed in the lab manual.

### 5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

**Adverse event**
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Serious adverse event**
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or

- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

**AEs considered "Always Serious"**
Cancers of new histology and exacerbations of existing cancer must be reported as a serious adverse event regardless of the duration between discontinuation of the trial medication and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described in section 5.3.6.2.

**Adverse events of special interest (AESIs)**
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, i.e. the potential for AEs based on the expected synergistic activity between the investigational drug and the TNFi background treatment. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see section 5.3.6.2. Instructions on how to handle AESI are provided in section 4.2.1.

The following are considered as AESIs:

- Infusion reactions including anaphylactic reaction
- Cytokine release syndrome
  - May manifest when a large numbers of immune cells becomes activated and releases inflammatory cytokines. Potentially life-threatening complications include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.

- Severe bacterial, fungal, and viral infections
- Infection with or reactivation of mycobacterium tuberculosis,
- Opportunistic infections
    - These include pneumocystis pneumonia, toxoplasmosa gondii encephalitis, cryptosporidiosis, microsporidiosis, mycobacterium avium; bacterial respiratory disease, bacterial enteric infection, mucocutaneous candidiasis, invasive mycoses, CMV, EBV, herpes simpex, varicella zoster; human herpesvirus 8, JC virus infection (adapted from http://aidsinfo.nih.gov/guidelines).
- Lymphoproliferative disorders
- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
    - an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, and/or
    - marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

**Intensity of AEs**
The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT (R13-3515). Refer to the ISF for intensity/severity classification. Intensity options are:

Grade 1 mild

Grade 2 moderate

Grade 3 severe

Grade 4 life-threatening

**Causal relationship of AEs**

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

**AE Collection**
The investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study:
  - all AEs (non-serious and serious) and all AESIs.

- After the individual patient's end of study:
  - the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

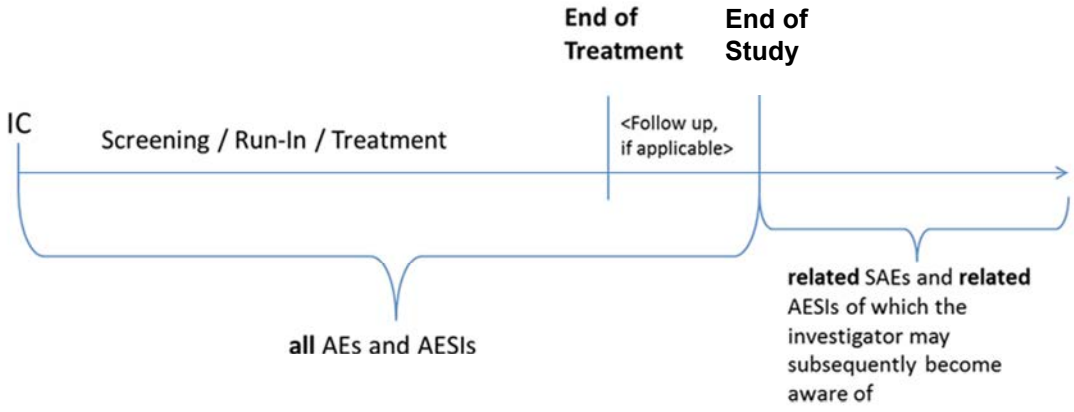


Figure 5.3.6.2: 1 AE reporting

The REP for BI 655130 is defined as 20 weeks after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

**AE reporting to sponsor and timelines**
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours ) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

**Information required**
For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, endoscopies if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of study must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

**Pregnancy**
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled into the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A o the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

## 5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

### 5.4.1 Assessment of Pharmacokinetics

BI 655130 concentrations will be reported descriptively. No PK parameters will be calculated.

PK data will be incorporated into a larger pharmacometric analysis with other trials of the BI 655130 project. Also, ADAs will be measured and their impact on PK will be assessed. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.

Refer to Flow Chart for the time points of PK and ADA sample collection. Date and exact time of drug administration and PK and ADA sampling will be recorded on eCRFs. On visits with study medication dosing, PK and ADA samples should be collected prior to administration of study drug.

### 5.4.2 Methods of sample collection

Optional use of plasma aliquots: Plasma samples may be used for further methodological investigations (ex: for future stability testing). However, only data for measuring the analyte and antibody responses to the analyte will be generated by these investigations. The PK study samples will be discarded after completion of the investigations but not later than 5 years after the final study report has been signed. Following the finalization of the ADA bioanalytical report, ADA aliquots will be transferred to long term storage for possible/optional ADA characterization in the future.

### 5.4.3 Analytical determinations

#### 5.4.3.1 Analytical determination of BI 655130 plasma concentration

BI 655130 concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).

#### 5.4.3.2 Assessment of ADA to BI 655130

The presence of ADA to BI 655130 will be assessed via their detection using a validated immunoassay in a tiered approach (screening, confirmatory, and titration analysis as appropriate).

### 5.4.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned.

## 5.5 ASSESSMENT OF BIOMARKER(S)

Biomarkers associated with Ulcerative Colitis and the IL-36 pathway will be assessed in biopsies, peripheral blood and stools from patients both pre and post treatment with BI 655130.

Blood samples (serum and plasma), stool samples and biopsies will be collected at time points indicated in the Flow Chart for the analysis of biomarkers. After completion of the study these samples may be used for not yet specified non-genetic biomarker analyses associated with autoimmune diseases as well as method development and evaluation. Samples will be stored for a maximum of 3 years (under consideration of local legislation) upon signature of the final study report.

Among the biomarkers, CRP and FCP are defined as Further Endpoints (see Section 5.1.3). Hence, their statistical analysis results are reported in the final CTR. For all the others, they may be reported in a separate biomarker report.

### 5.5.1 Biochemical and cellular biomarkers

Serum and plasma will be collected to assess changes in protein levels of disease specific markers such as but not limited to β defensin 2, neutrophil gelatinase associated lipocalin (NGAL), LL-37 and S-100 proteins (A7, A8, A12), CRP, IL-1β, IL-1RA, IL-1a, IL-6, IL-8, TNF, LCN2, IL-17A, IL-17F, IL-10, IL-12p70, IL-18, IL-22, IL-23, IFN-γ and VEGF both pre and post treatment with BI 655130. In addition, stool samples will be collected to assess changes in faecal levels of inflammatory markers such as but not limited to calprotectin and lactoferrin, pre- and at various time points post-treatment with BI 655130. These biomarkers are considered exploratory biomarkers and respective assays will need to be qualified to meet the required performance criteria.

Mucosal biopsies for histology and immunohistochemistry (IHC) analyses both pre and post treatment with BI 655130 will be performed at time points outlined in the Flow Chart and should be collected prior to administration of study drug at dosing on day 1 (baseline), Week 8 and EOT, Week 12. The markers planned to be assessed by IHC may include but not limited to MPO, TNFα, IL-1β, lipocalin 2/LCN2, ß defensin 2, CD3+ T lymphocytes, CD11+ and DC lamp (Dendritic Cells), CD68, and Mac-1 (on Macrophages).

Blood will be taken for flow cytometry analysis at visits indicated in the Flow Chart. Cellular biomarkers will be assessed using flow cytometry and will include markers of cell populations such as but not limited to neutrophils, macrophages, innate lymphoid cells and other lymphocyte subsets in whole blood.

The biomarker assay analysis of biochemical and cellular biomarkers samples will be performed in a staged approach. The initial analysis will focus on selected markers and time points (i. e. baseline, Week 12) and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.

### 5.5.2 Pharmacogenomic biomarkers

Mucosal biopsies for RNA expression will be collected at baseline, Week 8 and Week 12 to assess changes in gene expression levels both pre- and post-treatment with BI 655130.

For transcriptome-wide gene expression analysis RNA will be isolated from colon biopsies and analysed by RNA sequencing.

Whole blood samples for RNA expression will be collected at baseline, Week 8 and Week 12 to assess changes in gene expression levels both pre and post treatment with BI 655130. Therefore RNA will be isolated from peripheral blood and analysed by RNA sequencing.

### 5.5.3 Methods of sample collection

Biomarkers sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK/PD data), including addition of samples and visits. Such changes would be implemented via non-substantial CTP Amendments if possible.

Biopsies for RNA expression and IHC will be sampled in the colon during sigmoidoscopy at baseline and Week 8 and 12.

All biopsies for RNA sequencing analysis will be harvested in RNAlater kept at 4°C for at least 24 hours, and then stored at -20 °C.

For the assessment of RNA expression from whole blood, blood will be collected in PAXgene RNA tubes at time points indicated in the Flow Chart.

For the assessment of soluble protein biomarkers in serum, blood will be collected in a serum separation tube at time points indicated in the Flow Chart. For the assessment of soluble protein biomarkers in plasma, blood will be collected in a Sodium Heparin- anticoagulant blood drawing tube at the time points indicated in the Flow Chart. For flow cytometry, whole blood will be collected in an ACD drawing tube at the time points indicated in the Flow Chart.

Detailed instructions for biopsies, biomarkers sampling (serum, plasma, and stool), handling and shipment of samples are provided in the ISF or lab manual.

### 5.5.4 Analytical determinations

Total RNA from biopsies and whole blood will be isolated using an [redacted]
The integrity and quantity of RNA will be determined with a [redacted] and a [redacted]

Gene expression will be analysed using standard molecular genetic methods and technologies such as Next Generation Sequencing and TaqMan Real Time PCR.

The histopathological evaluation of the colon biopsies will be based on hematoxylin and eosin staining using the modified Robarts Histology Index (histologic activity score). Please refer to Appendix 10.3 for further details.

Serum, plasma and stool proteins and cell populations by flow cytometry will be analysed using established parameters for each analyte (protein) and the corresponding matrix (serum, plasma or stool) and cell subsets (flow cytometry).

Characteristics of the analytical methods for the analysis of colon biopsies, serum and plasma biomarkers and stool biomarkers will be given in detail in the clinical trial report or in an accompanying technical/biomarker report.

### 5.5.5 Biobanking

DNA Banking

One blood sample will be used for DNA Banking if participation and the separate informed consent is agreed upon by the patient as noted below. The DNA Banking sample, derived from the original blood sample, will be stored at the sponsor. The stored DNA may retrospectively be analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

Note: Participation in the DNA Banking sampling is voluntary and not a prerequisite for participation in the trial. The DNA Banking sample will be stored after separate informed consent is given in accordance with local ethical and regulatory requirements.

Methods and timing of sample collection

One (1) blood sample for DNA banking will be taken at Visit 2. A maximum of 8.5 mL blood will be collected per PAXgene DNA blood sampling tube for those patients who signed a separate informed consent concerning the Sample Banking part. The Paxgene Blood DNA tubes can be stored and shipped at room temperature within 14 days. If a longer storage and shipment period for Paxgene Blood DNA tubes is necessary, the blood samples have to be stored at a temperature of -20°C or below. Once frozen, thawing of the samples should be avoided. Detailed instructions for pharmacogenomic sampling, handling and shipment of samples are provided in the ISF.

## 5.6 OTHER ASSESSMENTS

Colonoscopy, Sigmoidoscopy

Colonoscopy and sigmoidoscopy will be performed according to standard of care. Central reading will be performed (for more information cf. ISF). Histopathology will be performed at a central laboratory.

Mucosal biopsies

Biopsies will be sampled from the regions with inflammation in the colon/rectum during all colonoscopies/sigmoidoscopies. The procedure for collecting and handling biopsies will be provided in the laboratory manual (for more information cf. ISF).

## 5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements in UC treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way.

Therefore, the appropriateness of all measurements applied in this trial is given.

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1 (Visit 2). If any of these visits has to be rescheduled, subsequent visits should follow the original visit date schedule from Day 1. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Regarding instructions for drug administration at missed or delayed visits please refer to Section 4.1.4.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and the respective protocol sections. Refer to Section 5 and 10 (Appendix) for explanations of procedures. Additional details on procedures at selected visits are provided below.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

Patient Reported Outcomes (PROs) should be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team.

The order of completion for PROs should be as follows, as applicable for each PRO at relevant visits according to the Flow Chart:

1) IBDQ

2) EQ-5D(-5L)

### 6.2.1 Screening and run-in period(s)

No trial procedures should be done unless the patient has consented to taking part in the trial.

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the screening log and be registered in IRT as a screened patient.

Screening visit (Visit 1a):

The Screening visit (Visit 1a) should normally take place no more than 35 days before Visit 2 and be complete no less than 8 days prior to Visit 2. At this visit, information will be collected for evaluation of trial eligibility as indicated in the Flow Chart.

*Baseline Conditions*

Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, endoscopy and any condition requiring therapy (excluding UC) will be reported on the baseline condition eCRF page.

*Demography*

Informed consent date, gender, age, race and ethnic origin will be collected in the eCRF page. Also, the patient's smoking and alcohol history will also be assessed. Information concerning race/ethnicity will be collected as it has been suggested that there might be race/ethnicity variations in the incidence, phenotypic manifestations and outcome of UC. Note: In some countries, race may not be collected.

*Medical and Surgical History*

Information on clinically significant previous and concomitant illnesses, other than UC, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening. For planned procedures/hospitalisations during the trial, documentation should be completed at the time of the screening. Regarding the UC, date of diagnosis, as well as previous and concomitant treatment for UC, will be recorded in the eCRF.

*Prior Therapies*

Prior therapies related to UC will be collected during screening.

*Ulcerative Colitis History*

A detailed history of UC, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations will be collected during screening.

*Blood sampling*

Blood samples will be taken for safety lab and infection screening (HBV, HCV, HIV and Quantiferon-TB). For women of childbearing potential, a serum pregnancy test will be performed.

*Stool sampling*

A stool sample will be collected to exclude existence of enteric pathogens. Stool sampling will be done for faecal calprotectin and lactoferrin, too.

*Patient diary*

Patients who are eligible at Visit 1a will receive a patient diary to be used for

1) daily reporting of stool frequency and rectal bleeding (blood in stool), as well as

2) daily intake of concomitant medication over the whole treatment period.

Patients will be instructed on the use of the diary during screening and treatment phase. The diary will be returned at EOS visit. Please refer to ISF for more information.

Visit 1b:

The Visit 1b should take place no more than 28 days and no less than 6 day prior to Visit 2. Visit 1b should be at least 1 day after Visit 1a.

A sigmoidoscopy (or full colonoscopy) with serial mucosal biopsies will be performed at this visit. A full colonoscopy must only be done, if no colonoscopy has been done in past 3 years in order to assess disease extent or to exclude cancer (if applicable per local guideline).

Based on the results from sigmoidoscopy or colonoscopy and clinical symptoms of the patient, a baseline Mayo score will be determined.

For a detailed description of the trial procedures at Visits 1a and 1b, please refer to the Flow Chart.

Patients who have a laboratory test value outside the range specified by the inclusion criteria may have the test repeated to determine eligibility. The result must be available prior to Visit 2 (Day 1).

The time window for Visit 1a and 1b may be extended at the discretion of the CML in conjunction with the TCM on a case by case basis or re-screening is performed.

Re-screening will be allowed once. Patients who fail screening following Visit 1a and 1b assessments should be registered as a screen failure in IRT.

### 6.2.2 Treatment period(s)

The treatment period is from Visit 2 to End of Treatment (EOT) Visit.

Study related procedures will be performed as specified in the Flow Chart.

*Pregnancy testing*

Urine pregnancy testing for all women of child-bearing potential will be conducted on-site approximately every four weeks and must be negative to continue treatment. The pregnancy testing should be done prior to administration of study drug. A positive urine test must be confirmed with a serum pregnancy test.

*Blood sampling*

Blood sampling (e.g., for safety lab, biomarkers) should be the last procedure prior to any study drug administration and prior to sigmoidoscopy if applicable.

*Sigmoidoscopies*

Sigmoidoscopies will be done after blood sampling and prior to study drug administration. During sigmoidoscopies, biopsies will be taken for endpoint evaluation at time-points as indicated in the Flow Chart. Please refer to ISF for further information on the collection of biopsies.

*PK and ADA sampling*

At visits with study drug administration, blood sampling for PK and ADA assessments should be done pre-dose within 2 hours prior to start of i.v. infusion.

*Clinical monitoring after study drug administration:*

At all visits with study drug administration, vital signs will be assessed pre-dose, and at approximately 5 and 120 minutes after end of infusion.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after doses administered. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

*Unscheduled visits*

The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, sigmoidoscopy or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

*Concomitant medication review*

Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the Flow Chart. These data will be obtained at scheduled or unscheduled. trial visits based on information provided in the patient diaries, provided spontaneously by the patient or as a result of questioning the patient.

### 6.2.3 Follow Up Period and Trial Completion

For all randomised patients, termination of trial medication and trial completion must be recorded on the corresponding eCRF.

A sigmoidoscopy must be performed if a clinical flare of UC occurs during follow up period. This can be performed within an extra un-scheduled visit.

Early treatment discontinuation:

Patients who discontinue treatment prior to the regular EOT visit, should follow the Flow Chart until EOT visit, Week 12. These patients do have the option to do EOS visit earlier, i.e. 20 weeks (corresponding to residual effect period of study drug) after last study drug administration. Until then they should follow the Flow Chart.

Trial completion:

Patients who finish the randomised treatment period will return to the clinic for follow-up visits. Completion is defined as a patient having reached the EOS visit.

Further treatment after the end of the trial:

At the end of the trial patients will be treated for their UC at the discretion of the investigator, according to UC guidelines (e.g. ECCO guidelines, R17-0243).

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

This trial is a study of proof-of-concept in patients with ulcerative colitis. It is designed as a randomised, double-blind, and placebo-controlled trial with 2 parallel groups (1 dose of BI 655130 and placebo).

The primary objective of this trial is to explore the safety and efficacy of BI 655130 in comparison to placebo in patients with ulcerative colitis.

Mucosal healing at Week 12 is the primary efficacy endpoint for this trial. Mucosal healing is defined as achieving a Mayo modified endoscopic subscore (mESS) ≤1.

Randomisation will be stratified based on concomitant use (yes, no) of infliximab. However, due to the low number of patients to be recruited into this trial, the primary analysis will be performed without consideration of stratification. The effects of the stratification variable on the primary endpoint will be assessed only in exploratory analyses.

Considering the above design characteristics, as well as the binary nature of the primary endpoint, this trial is designed to show an increase in the proportion of patients who demonstrate mucosal healing for BI 655130 relative to placebo via the unadjusted risk difference estimate.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

There will be no formal hypothesis testing performed in this trial.

As an exploratory Phase II trial in patients with ulcerative colitis, inferences concerning the efficacy of BI 655130 will be based on the magnitude of the observed difference(s) in the proportion of patients demonstrating mucosal healing at Week 12 compared to placebo, as well as on other secondary efficacy endpoints.

A sample size justification can be found in Section 7.7.

## 7.3 PLANNED ANALYSES

The efficacy analyses will be performed for the FAS which is based on the intent-to-treat principle, and comprises all participants who were randomised, received at least one dose during the trial, and had a baseline measurement for the primary endpoint. Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation). Safety analyses on patients who were randomised and received at least one dose during the trial will be based on the actual treatment received at the randomisation visit; this set of patients is called the Safety Set (SAF). All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF.

Important violations of the protocol will include key inclusion and exclusion violations, incorrect medications taken, compliance with study medication, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to un-blinding of the database for the primary Week 12 analysis. A per-protocol set (PPS) will be defined as a subset of the FAS which excludes all patients with a violation that potentially affects the Week 12 efficacy assessment.

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

For continuous secondary or further endpoints, mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment and visit, presence or absence of use of infliximab (yes/no), as well as the treatment-by-visit interaction, and continuous, fixed covariates of baseline "endpoint" and baseline-by-visit interaction. An unstructured covariance structure will be used to model the within-patient measurements. Exploratory confidence intervals will be based on least-squares mean differences to placebo using a two-sided $\alpha = 0.05$.

This is an exploratory trial and formal confirmatory statistical testing will not be performed.

### 7.3.1 Primary endpoint analyses

The evaluation of endoscopic activity at Week 12 is the primary objective for efficacy in this trial and is described using the proportion of patients with mucosal healing at this time-point based on results obtained from central reading.

The primary analysis of the unadjusted absolute risk difference versus placebo will be calculated simply as the difference in the observed proportion of patients with mucosal healing at Week12, for the FAS. A 95% Newcombe confidence interval around this difference will also be provided.

Exploratory analyses of the primary endpoint will include, in the absence of model convergence issues due to occurrence of low cell frequencies, the difference in the proportion of patients with mucosal healing at Week 12 between BI 655130 and placebo, for the FAS, using a logistic regression approach with a logit link. Fixed classification effects will include treatment and presence or absence of use of infliximab (yes/no). The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale, with the confidence interval calculated using the cumulative distribution function method of Reeve [R16-4414]; further details will be provided in the TSAP.

Secondary analyses of the primary endpoint will include:

- Sensitivity analyses utilizing different patients sets (such as the PPS), as well as alternative methods for the handling of missing data as described in section 7.5;

- Exploration of the relationship between various demographic or baseline characteristics data and the primary endpoint will be performed via graphical methods as well as using a logit link with [redacted]

Further details will be provided in the trial statistical analysis plan.

### 7.3.2 Secondary endpoint analyses

For the secondary binary endpoints related to efficacy, for the FAS, the unadjusted absolute risk difference versus placebo will be calculated and a 95% Newcombe confidence interval around this difference will also be provided.

For secondary continuous endpoints, mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach (see section 7.3).

For the stool frequency and rectal bleeding items reported in the patient diary, an average of the last 3 non-missing daily assessments collected within the last 7 days prior to the applicable visit will be used for the determination of clinical remission. If the patient undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscores on that day(s) should be considered to be missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both on the day of and the day after the endoscopy.

[redacted]

### 7.3.4 Safety analyses

The safety set, described in section 7.3, will be used to perform all safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect

period (REP) is defined as 20 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Drug related AEs will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

In addition, the frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

### 7.3.5 Pharmacokinetic and pharmacodynamic analyses

BI 655130 concentrations will be reported descriptively. No PK parameters will be calculated.

### 7.3.6 Biomarker analysis

The patient set for the evaluation of biomarker assessments (BioMarker Set [BMS]) will include all treated patients that provide at least one observation for at least one biomarker matrix. It will be decided in the Report Planning Meeting or the Medical Quality Review Meeting whether patients having important protocol violations that could have a significant impact on biomarker analyses are to be excluded from the BMS. Excluded patients will be listed with their individual parameter values.

The statistical analysis for biomarker assessments is mainly descriptive. Summary statistics and summary plots are produced for each assessment at each time point, and for changes from baseline when appropriate.

In particular, for assessments measured on a continuous scale, means, standard deviations, quantiles, and percentiles are produced. Confidence intervals for the mean estimates are calculated at 95% confidence levels. Changes from baseline at each time point are reported similarly.

Summary plots for continuous variables include, but are not necessarily limited to, dot-plot for each assessment at each time point; side-by-side boxplot and line graph for selected variables over time.

For assessments that are categorical or ordinal in nature—for example, results from histopathological and IHC evaluation (Section 5.5.4), frequency tables are produced. Bar-plots are presented. Shift-tables are also produced for each variable between baseline and each post-baseline value, if feasible.

Correlations between biomarkers and clinical endpoints are also examined descriptively. Scatter plots are produced at each time point. Due to the small sample size, no hypothesis testing will be conducted; hence, no confirmative p-values will be reported.

#### 7.3.6.1 Analysis of cellular and biochemical biomarkers

Descriptive statistics and plots as described above are provided. Further details will be discussed in the TSAP.

#### 7.3.6.2 Pharmacogenomic analyses

Changes in the gene expression profile of mucosal biopsy and whole blood markers from baseline to post-baseline will be summarized and described for selected genes. Only significantly up- or down-regulated genes are reported. Thresholds for defining significantly up- and down-regulations are given in the TSAP.

Graphical displays such as heatmaps are generated for visual assessments of the changes in gene regulations between treatment and placebo group.

Spearman's correlation coefficients between change from baseline in clinical endpoints (e.g. modified PGA) and mucosal biopsy or whole blood RNA expression levels of selected genes will be calculated at each time point. Details will be discussed in the TSAP.

## 7.4 INTERIM ANALYSES

In order to ensure the patient's safety during the trial, a fully external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC SAP which describes the analyses required for assessment by the DMC will be produced and finalized prior to first patient randomised into the trial. Further details will be provided in a DMC charter.

Once all randomised patients have completed the first 12 weeks of study, a partial database lock may be performed in order that a fast track analysis of primary and selected secondary and safety endpoints be done; a second data lock would then be done for the remaining efficacy and safety data collected up to Week 12. If fast-track analysis is not performed, a single database lock will be done for safety and efficacy data collected up to Week 12. At this time, the final analysis of these data through Week 12 will be performed. Since the study is planned to continue through an additional 24 weeks of further follow-up, and will remain blinded, a logistics plan will be developed in order to protect the integrity of the ongoing trial data and reporting subsequent to treatment un-blind for both the possible fast track and the

complete Week 12 primary analysis. Details of the analysis to be performed for the Week 12 data will be described in the TSAP which is planned to be finalized prior to achieving database lock for the Week 12 analysis.

An analysis of the entire trial data will be performed once all randomized patients have completed the 36 weeks of the study. At this time, the database will be locked, and official unblinding of the trial will be performed. Details of the analysis to be performed for the completed trial through 36 weeks (End of Study Visit) will be described in the TSAP which is planned to be finalized prior to achieving database lock for the Week 12 analysis.

All analyses are planned to be documented in a clinical trial report which is to be prepared at the end of the trial.

## 7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

With respect to safety evaluations, it is not planned to impute missing values.

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed:

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success;
- Otherwise, impute as a failure to achieve a response (i.e. NRI [No Response Imputation]).

If a patient takes a rescue medication (as defined in section 4.2.1) for the treatment of ulcerative colitis prior to observing the primary endpoint for this trial, then all data subsequent to the intake of such rescue will be considered to represent a failure to achieve a response. Further details on what constitutes a rescue intake with potential impact on efficacy outcomes will be described in the TSAP.

As a sensitivity analysis, the primary endpoint will be repeated using the NRI approach but including also all values obtained following rescue intake.

Further sensitivity analyses to assess the robustness of the results on the primary endpoint may be performed and as such will be described in the TSAP.

For secondary efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

## 7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment. Patients will be randomised in a 2:1 ratio to BI 655130 and placebo with stratification according to the concomitant use of infliximab (yes or no). BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

## 7.7 DETERMINATION OF SAMPLE SIZE

Calculations were performed using simulations performed via the Statistical Analysis Systems (SAS®) software, version 9.4.

The study is intended to show an increase of BI 655130 over placebo in terms of the difference in proportion of patients achieving mucosal healing at Week 12 (see primary endpoint). There is currently no clinical trial data available in the published literature that describes a placebo response on the mucosal healing in the population of patients with ulcerative colitis at Week 12 to be recruited into this trial. The success probability for the primary endpoint on this PoCC trial has, therefore, been derived under the assumption that the difference between BI 655130 and placebo is 0.30 and that a total N of 30 patients (fixed according to feasibility considerations) will be studied in a 2:1 ratio (that is 20 to receive BI 655130 versus 10 patients to receive placebo).

Simulations in SAS® were used to derive estimates of the probability that a single trial would demonstrate an observed difference in proportions between BI 655130 and placebo that was equal or greater than a defined threshold under a positive scenario whereby the expected difference in proportions is 0.3 in favour of BI 655130. For identifying such a target threshold, a minimum probability of 0.80 was defined. For each trial simulation, the response for each patient on each treatment was generated using a binomial distribution utilizing the expected response rates as noted in table below, and the trial observed proportions were then directly compared. A total of 10,000 trial simulations were performed. Note that the probability of a false positive declaration given the specified target threshold, so called negative scenario, was also determined.

Table 7.7: 1 Probability of Achieving the Threshold Difference in Treatments given Expected Treatment Response Rates on Mucosal Healing and a Total Sample Size of 30 Patients

| **Population Response Rate** | | **Expected Response Difference** | **Total N (2:1)** | **Threshold (Observed Difference)** | **Probability Threshold Exceeded[1]** | **False Positive Rate (%)[2]** |
|---|---|---|---|---|---|---|
| **Active BI** | **Placebo** | | | | | |
| **Response Difference =0.30** | | | | | | |
| 0.35 | 0.05 | 0.3 | 30 | 0.20 | 78% | 1% |
| 0.40 | 0.10 | 0.3 | 30 | 0.20 | 75% | 5% |
| 0.35 | 0.05 | 0.3 | 30 | 0.15 | 89% | 5% |
| 0.40 | 0.10 | 0.3 | 30 | 0.15 | 84% | 14% |
| 0.35 | 0.05 | 0.3 | 30 | 0.10 | 94% | 17% |
| 0.40 | 0.10 | 0.3 | 30 | 0.10 | 90% | 27% |

[1] Assuming the expected response rate difference, the probability that the observed BI 655130 response rate exceeds that of placebo by at least the threshold amount is displayed.

[2] The probability that the observed BI 655130 response rate exceeds that of placebo by at least the threshold amount under the negative scenario that treatments are equal.

In summary, for a total N of 30 patients, a 2:1 randomisation ratio to BI 655130 and placebo, then under the assumption of a target difference between BI 655130 and placebo of 0.30 for the proportion of responders on the primary endpoint, then this trial will be able to detect with probability of 0.84, a superior response rate, versus placebo, which is at least ≥ 0.15 in magnitude in favour of BI 655130 when the population placebo response rate is no larger than 0.10. The corresponding false positive error rate is 14% (one-sided). Given that only two treatments are to be compared, no correction for multiplicity is required.

# 8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP*.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF (Investigator Site File).

## 8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## 8.3 RECORDS

Case Report Forms (CRF) for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

### 8.3.1 Source documents

For adverse events, an end date may not always be available (e.g. due to hospital discharge and later recovery, or change in treating physician), but should be recorded in the source if known.

For eCRF all data need to be derived from source documents, which need to be available on-site (this could be for example physician's notes in patient files, printouts, patient diaries)

Describe how the data are recorded, e.g. direct entry into the paper CRF / print-outs (e.g. laboratory data), data captured and stored electronically, or data transcribed into the CRF.

Describe also the key aspects of the data flow, including the role of external vendors, if applicable.

A list of expected source documents is to be provided in this section based on the trial specific methodology. Additions should be made as applicable. This may comprise

- Originals or copies of imaging diagnostics
- ECG results (original or copies of printouts)
- EEG results (original or copies of printouts)
- Lung function test results
- Endoscopic findings
- Other results based on outputs of medical machinery equipment, etc.
- Patient reported outcome forms (including diary) and corresponding investigator assessment form.

If defined in the protocol, additional records may need to be requested from the investigator, e.g. information from any referral physicians on patient history relevant for AE reporting or data required in connection with outcome event collection in outcome studies.

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)

- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).

- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

### 8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

### 8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

## 8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

The rights of the trial patient to privacy and protection of the data / patient notes obtained during the trial have to be ensured in accordance with local laws and regulations. Procedures for data handling and data protection need to be described in the patient information and informed consent form.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will

be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

### 8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)

- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

- Samples and data are used only if an appropriate informed consent is available.

## 8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

**The end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

**Temporary halt of the trial** is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

**Suspension of the trial** is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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# 10. APPENDICES

## 10.1 DEFINITIONS OF CLINICAL RESPONSE/REMISSION

| MCS subscore | RBS | mESS | SFS | PGA | Total |
|---|---|---|---|---|---|
| **Clinical remission** | ≤1 | ≤1 | ≤1 | ≤1 | ≤2 |
| **Modified clinical remission** | 0 | ≤1 | 0<br>or<br>1 and drop ≥1 from baseline | n.a. | ≤2 |
| **Partial clinical remission** | ≤1 | n.a. | ≤1 | ≤1 | ≤2 |
| **Clinical response** | ≤1<br>Or<br>Reduction ≥1 | - | - | - | Reduction ≥3 and 30%<br>or<br>Reduction ≥2 and 25% if mESS n.a. |

Abbreviations: RBS – rectal bleeding score; mESS – modified endoscopic subscore; SFS – stool frequency score; PGA – physician's global assessment;

## 10.2 MAYO SCORING SYSTEM FOR THE ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

The Mayo score (R16-4416) is a composite disease activity score consisting of four items or subscores: stool frequency (relative to normal), rectal bleeding, physician's global assessment, and endoscopic appearance. As proposed by FDA draft guidance (R17-0038), the endoscopic subscore is modified so that a value of 1 does not include friability. The overall range of the total Mayo score is 0-12 (higher scores being worse) and each subscore has a range of 0-3 (Table 10.2: 1). At visits without sigmoidoscopy, a partial Mayo score without endoscopy subscore will be assessed. The overall range of this partial Mayo score is 0-9.

In addition, based on FDA's recommendation (R17-0038), a modified Mayo score will be assessed, which excludes physician's assessment. The overall range of the modified Mayo score is 0-9.

The scores for stool frequency and rectal bleeding will be calculated as an average of the last 3 non-missing entries (from the patient daily diary) within the week prior to each applicable visit. If the patient undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscore for that day(s) should be considered missing. In addition, the stool frequency and rectal bleeding subscore will be considered missing for the day of and the day after all endoscopies.

The endoscopic appearance score will be assessed by a central reader, who is independent from the investigator.

Table 10.2: 1 Mayo score (adopted from Schroeder et al, 1987 (R16-4416)

| Components | Subscore | Severity | Score |
|---|---|---|---|
| **CLINICAL RESPONSE** (Patient's Symptoms) | Stool Frequency[a] (daily) | Normal number of stools for patient | 0 |
| | | 1 to 2 stools more than normal | 1 |
| | | 3 to 4 stools more than normal | 2 |
| | | ≥5 stools more than normal | 3 |
| | Rectal Bleeding[b] (daily) | No blood seen | 0 |
| | | Streaks of blood with stool | 1 |
| | | Obvious blood with stool | 2 |
| | | Blood alone passes | 3 |
| | Physician's Global Assessment[c] | Normal | 0 |
| | | Mild disease | 1 |
| | | Moderate disease | 2 |
| | | Severe disease | 3 |
| **MODIFIED ENDOSCOPIC RESPONSE** (Objective Evidence of Inflammation) | Endoscopic Appearance[d] | Normal | 0 |
| | | Mild disease | 1 |
| | | Moderate disease | 2 |
| | | Severe disease | 3 |

a Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

b The daily bleeding score represents the most severe bleeding of the day.

c The physician's assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

d Modified endoscopic appearance: 0 (normal), Mild (erythema, decreased vascular pattern), Moderate (marked erythema, loss of vascular pattern, any friability, erosions), Severe (spontaneous bleeding, ulceration).

## 10.3 HISTOLOGIC ACTIVITY SCORE

The Robarts histopathology index is a histologic activity score (R16-4652). The total score ranges from 0 (no disease activity) to 33 (severe disease activity).

Table 10.3: 1 Robarts Histopathology Index (RHI) by components

| Component | |
|---|---|
| Intercept | |
| Chronic inflammatory infiltrate | 0=No Increase |
| | 1=Mild but unequivocal increase |
| | 2=Moderate increase |
| | 3=Marked increase |
| Lamina propria neutrophils | 0=None |
| | 1=Mild but unequivocal increase |
| | 2=Moderate increase |
| | 3=Marked increase |
| Neutrophils in epithelium | 0=None |
| | 1=<5% crypts involved |
| | 2=<50% crypts involved |
| | 3=>50% crypts involved |
| Erosion or ulceration | 0=No erosion, ulceration, or granulation tissue |
| | 1=Recovering epithelium + adjacent inflammation |
| | 1=Probably erosion-focally stripped |
| | 2=Unequivocal erosion |
| | 3=Ulcer or granulation tissue |

Based on this, the RHI will be calculated as follows:

RHI = 1 x chronic inflammatory infiltrate level (0-3) + 2 x lamina propria neutrophils (0-3) + 3 x neutrophils in epithelium (0-3) + 5 x erosion or ulceration (0-3)

## 10.4 EQUIVALENT DOSES OF CORTICOSTEROIDS

| Drug | Equivalent dose (mg) | Conversion factor |
|---|---|---|
| Prednisone | 5 | X 1 |
| Prednisolone | 5 | X 1 |
| Triamcinolone | 4 | X 1.25 |
| 6-Methylprednisolone | 4 | X 1.25 |
| Dexamethasone | 1 | X 5 |
| Betamethasone | 0,75 | X 6.7 |
| Fluocortalon | 5 | X 1 |
| Cloprednol | 3,75-5 | X 1.0-1.5 |
| Deflazacort | 6 | X 0.8 |
| Cortisol (hydrocortisone) | 20 | X 0.25 |
| Cortisone | 25 | X 0.20 |
| Budesonide | 1,125 | X 4.4 |

## 10.5 PATIENT REPORTED OUTCOMES

### 10.5.1 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ (R97-3472) is a 32-item self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224 with higher scores indicating better outcomes.

### 10.5.2 EQ-5D-5L

The EQ-5D(-5L) is a standardized instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D(-5L) questionnaire captures two basic types of information, an overall health rating using a visual analog scale and a descriptive “profile,” or “health state”. The health state is converted to a single weighted index score by applying coefficients from a validated value set. The index score is used in both clinical and economic evaluations of health care. These two basic types of information cannot be combined and will be reported separately.

The health state index measures five health dimensions. The health states for each respondent are converted into a single index number using a specified set of country-specific weights. A higher score indicates a more preferred health status with 1.0 representing perfect health and 0 representing death. A missing answer on any one question leads to a missing overall score.

For purposes of the analyses for this study, all patients’ EQ-5D(-5L) index scores will be calculated using the UK weights1. The VAS asks respondents to rate their present health status on a 0 - 100 visual analog scale, with 0 labelled as “Worst imaginable health state” and 100 labelled as “Best imaginable health state.” The VAS score is determined by observing the point at which the subject’s hand drawn line intersects the scale.

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 13 Jun 2017 |
| **EudraCT number** | | 2016-004572-21 |
| **BI Trial number** | | 1368.10 |
| **BI Investigational Product(s)** | | BI 655130 |
| **Title of protocol** | | Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | X |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | |
| | | |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Addition of objective safety and secondary endpoint adverse events. |
| **Rationale for change** | | Clarification that safety assessment is an objective of this study because in particular safety is a central part of Phase IIa studies. |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |

| | | |
|---|---|---|
| **Description of change** | | Change time point of diagnosis of ulcerative colitis to ≥ 5 months prior to screening. |
| **Rationale for change** | | Clarification of minimum duration of disease in order to allow for stable TNFi treatment for ≥ 4 months prior to randomisation. Induction phase of TNFi treatment is not seen as stable TNFi treatment. |
| **Section to be changed** | | FLOW CHART |
| **Description of change** | | HBV-DNA test was added at baseline (Visit 2) and EOT (end of treatment) Visit. |
| **Rationale for change** | | HBV-DNA monitoring was added to detect any cases of HBV (hepatitis B virus) infection reactivation in occult HBV infected patients. |
| **Section to be changed** | | 2.2 TRIAL OBJECTIVES |
| **Description of change** | | Update safety as an objective of this study. |
| **Rationale for change** | | Clarification that safety assessment is an objective of this study because in particular safety is a central part of Phase IIa studies. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Change time point of diagnosis of ulcerative colitis to ≥ 5 months prior to screening. |
| **Rationale for change** | | Clarification of minimum duration of disease in order to allow for stable TNFi treatment for ≥ 4 months prior to randomisation. Induction phase of TNFi treatment is not seen as stable TNFi treatment. |
| **Section to be changed** | | 5.1.2 Secondary Endpoint(s) |
| **Description of change** | | Addition of “treatment emerging adverse events” to the list of secondary endpoints. |
| **Rationale for change** | | Safety measurements are included to the list of secondary endpoints to support the study objectives. |
| **Section to be changed** | | Table 5.3.3: 2 Laboratory tests |

| | | |
|---|---|---|
| **Description of change** | | HBV-DNA test was added at baseline (Visit 2) and EOT (end of treatment) Visit. |
| **Rationale for change** | | HBV-DNA monitoring was added to detect any cases of HBV (hepatitis B virus) infection reactivation in occult HBV infected patients. |
| **Section to be changed** | | 5.5.5 Biobanking |
| **Description of change** | | Deletion of last paragraph. |
| **Rationale for change** | | This is an administrative change to correct typographical errors. |
| **Section to be changed** | | 7.3.2 Secondary endpoint analyses |
| **Description of change** | | Clarification of secondary endpoint analysis related to efficacy. |
| **Rationale for change** | | Clarification needed, because safety measurements are included to the list of secondary endpoints. |
| **Section to be changed** | | Table 10.2: 1 |
| **Description of change** | | Deletion of “granulariy” from footnote d. |
| **Rationale for change** | | Correction of assessment of modified endoscopic response. |
| **Section to be changed** | | 10.4. EQUIVALENT DOSES OF CORTICOSTEROIDS |
| **Description of change** | | Deletion of “16-Methylprednisolone” from the table. |
| **Rationale for change** | | This is an administrative change to correct typographical errors. |
| **Section to be changed** | | 10.4. EQUIVALENT DOSES OF CORTICOSTEROIDS |
| **Description of change** | | Addition of equivalent doses of budenoside. |
| **Rationale for change** | | Update table with information for budenoside. |

| | | |
|---|---|---|
| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | 13 Dec 2017 |
| **EudraCT number** | | 2016-004572-21 |
| **BI Trial number** | | 1368.10 |
| **BI Investigational Product(s)** | | BI 655130 |
| **Title of protocol** | | Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | X |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Inclusion criterion 2: deletion of lower body weight limit of 60 kg. |
| **Rationale for change** | | A lower body weight limit is not needed any more. |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Addition of information for inclusion criterion 4: unchanged dose includes unchanged dose and dosing interval. |
| **Rationale for change** | | Clarification that unchanged dose consists of unchanged dose and unchanged dosing interval. |
| **Section to be changed** | | FLOW CHART |

| | | |
|---|---|---|
| **Description of change** | | Addition of sigmoidoscopy as baseline endoscopy. Colonoscopy is only required if not done within past 3 years. |
| **Rationale for change** | | A sigmoidoscopy is done at baseline and a colonoscopy has only to be done if not done within past 3 years. |
| **Section to be changed** | | FLOW CHART |
| **Description of change** | | A separate line for HBV-DNA monitoring was added. |
| **Rationale for change** | | This is an administrative change in order to emphasize time points for HBV-DNA monitoring. |
| **Section to be changed** | | 1.2 DRUG PROFILE |
| **Description of change** | | Update information for study 1368.1 and 1368.2. Addition of information from population pharmacokinetic modelling. |
| **Rationale for change** | | Update information from phase I studies and providing rationale why lower body weight limit is not needed anymore. |
| **Section to be changed** | | 2.3 BENEFIT - RISK ASSESSMENT |
| **Description of change** | | Update information for phase I studies and studies with BI 655130 in other indications. Addition of information from population pharmacokinetic modelling. |
| **Rationale for change** | | Update safety information of BI 655130 and providing rationale why lower body weight limit is not needed anymore. |
| **Section to be changed** | | 2.3 BENEFIT - RISK ASSESSMENT |
| **Description of change** | | Update information of risks by endoscopies. |
| **Rationale for change** | | A sigmoidoscopy is done at baseline and a colonoscopy has only to be done if not done within past 3 years. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Inclusion criterion 2: deletion of lower body weight |

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|---|---|---|
| | | limit of 60 kg. |
| **Rationale for change** | | A lower body weight limit is not needed anymore. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Addition of information for inclusion criterion 4: unchanged dose includes unchanged dose and dosing interval. |
| **Rationale for change** | | Clarification that unchanged dose consists of unchanged dose and unchanged dosing interval. |
| **Section to be changed** | | 4.1.2 Selection of doses in the trial |
| **Description of change** | | Deletion of lower body weight limit of 60 kg. |
| **Rationale for change** | | A lower body weight limit is not needed anymore. |
| **Section to be changed** | | 6.2.1 Screening and run-in period(s) |
| **Description of change** | | Update information for endoscopies. |
| **Rationale for change** | | A sigmoidoscopy is done at baseline and a colonoscopy has only to be done if not done within past 3 years. |
| **Section to be changed** | | 9.1 PUBLISHED REFERENCES |
| **Description of change** | | Update references. |
| **Rationale for change** | | Reference was added. |
| **Section to be changed** | | Update references. |
| **Description of change** | | 9.2 UNPUBLISHED REFERENCES |
| **Rationale for change** | | Administrative change to correct title of investigator’s brochure. |

| | | |
|---|---|---|
| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | 04 Mar 2019 |
| **EudraCT number** | | 2016-004572-21 |
| **BI Trial number** | | 1368.10 |
| **BI Investigational Product(s)** | | BI 655130 |
| **Title of protocol** | | Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | X |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Inclusion criterion 1: Change upper limit of age from 60 years to 75 years. |
| **Rationale for change** | | Upper age limit is changed to 75 years in order to facilitate recruitment into the study. |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Inclusion criterion 2: Change upper limit of body weight from 100 kg to 120 kg. |
| **Rationale for change** | | To allow for inclusion of patients up to 120 kg weight in order to facilitate recruitment into the study. |

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|---|---|---|
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Inclusion criterion 4: Add information for possibility of TNFi treatment with adalimumab and golimumab with doses unchanged for ≥2 months. Patients may or may not have received up to 2 different prior TNFi treatments. |
| **Rationale for change** | | TNFi treatment with golimumab is possible, too. TNFi treatment with adalimumab and golimumab needs to be on stable dose ≥2 months prior to randomisation only, because of their more frequent dosing interval in comparison to infliximab. Patients do not need to be on their first TNFi treatment, but may have received up to 2 different prior TNFi treatments. These changes are made in order to facilitate recruitment into the study. |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Endpoints: Change of primary endpoint to "mucosal healing (MCS mESS ≤1) at Week 12" instead "at Week 8". Change of secondary endpoint to "clinical remission based on Mayo score (total MCS ≤2 points, and all subscores ≤1 point) at Week 12" instead "at Week 8". Change of secondary endpoint to "histological remission (Robarts (RHI) score ≤6) at Week 12" instead "at Week 8". Delete endpoint "mucosal healing (MCS mESS ≤1) at Week 8". |
| **Rationale for change** | | Primary endpoint and secondary endpoints are changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | CLINIAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Statistical methods: Update information for primary objective to be evaluated at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is |

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|---|---|---|
| | | now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 2.3 BENEFIT - RISK ASSESSMENT |
| **Description of change** | | Potential benefits: Delete information for “2nd line” TNFi. |
| **Rationale for change** | | TNFi treatment may be 2nd or 3rd TNFi treatment as rescue treatment, because inclusion criterion 4 is changed. |
| **Section to be changed** | | 2.3 BENEFIT - RISK ASSESSMENT |
| **Description of change** | | Potential risks: Add information that body weight up to 120 kg is not expected to affect PK and efficacy of study drug. |
| **Rationale for change** | | Upper weight limit is changed to 120 kg. |
| **Section to be changed** | | 2.3 BENEFIT - RISK ASSESSMENT |
| **Description of change** | | Potential risks: Correction of “exudative”. |
| **Rationale for change** | | This is an administrative change to correct a typographical error. |
| **Section to be changed** | | 3.1 OVERALL TRIAL DESIGN AND PLAN |
| **Description of change** | | Update information for primary endpoint assessment at Week 12 instead at Week 8. Delete sentence about secondary endpoint assessment after 12 weeks. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 3.1 OVERALL TRIAL DESIGN AND PLAN |
| **Description of change** | | Figure 3.1: 1: Update figure for primary endpoint and TNF inhibitor. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8. TNFi treatment with adalimumab and golimumab needs to be on stable dose ≥2 months |

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|---|---|---|
| | | prior to randomisation. |
| **Section to be changed** | | 3.1.1 Administrative structure of the trial |
| **Description of change** | | Update information for DMC, i.e. now fully external DMC. |
| **Rationale for change** | | DMC is changed from a partially external to a fully external DMC. |
| **Section to be changed** | | 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) |
| **Description of change** | | Update information and rationale for prior and current TNFi treatment. |
| **Rationale for change** | | TNFi treatment with golimumab is possible, too. Patients do not need to be on their first TNFi treatment, but may have received up to 2 different prior TNFi treatments. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Inclusion criterion 1: Change upper limit of age from 60 years to 75 years. |
| **Rationale for change** | | Upper age limit is changed to 75 years in order to facilitate recruitment into the study. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Inclusion criterion 2: Change upper limit of body weight from 100 kg to 120 kg. |
| **Rationale for change** | | To allow for inclusion of patients up to 120 kg weight in order to facilitate recruitment into the study. |
| **Section to be changed** | | 3.3.2 Inclusion criteria |
| **Description of change** | | Inclusion criterion 4: Add information for possibility of TNFi treatment with adalimumab and golimumab with doses unchanged for ≥2 months. Patients may or may not have received up to 2 different prior TNFi treatments. |
| **Rationale for change** | | TNFi treatment with golimumab is possible, too. |

| | | |
|---|---|---|
| | | TNFi treatment with adalimumab and golimumab needs to be on stable dose ≥2 months prior to randomisation only, because of their more frequent dosing interval in comparison to infliximab. Patients do not need to be on their first TNFi treatment, but may have received up to 2 different prior TNFi treatments. These changes are made in order to facilitate recruitment into the study. |
| **Section to be changed** | | 3.3.3 Exclusion criteria |
| **Description of change** | | Exclusion criterion 3: Prior use of more than two different TNF inhibitors is not allowed. |
| **Rationale for change** | | Patients do not need to be on their first TNFi treatment, but may have received up to 2 different prior TNFi treatments. This change is made in order to facilitate recruitment into the study. |
| **Section to be changed** | | 3.3.4.1 Withdrawal from trial treatment |
| **Description of change** | | Update information for primary endpoint assessment at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 5.1.1 Primary Endpoint(s) |
| **Description of change** | | Change of primary endpoint to “mucosal healing (MCS mESS ≤1) at Week 12” instead “at Week 8” |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 5.1.2 Secondary Endpoint(s) |
| **Description of change** | | Delete several endpoints at Week 8 and move to further endpoints. |
| **Rationale for change** | | Endpoints at Week 8 are changed from secondary |

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|---|---|---|
| | | endpoints to further endpoints, because initial data indicate a potential for slower onset of action for this MoA. |
| **Section to be changed** | | 5.5.1 Biochemical and cellular biomarkers |
| **Description of change** | | Correction of “Week 8” and “Week 12”, i.e. spelling with capital letter. |
| **Rationale for change** | | These are administrative changes to correct typographical errors. |
| **Section to be changed** | | 5.5.1 Biochemical and cellular biomarkers |
| **Description of change** | | Add information that biomarker assay analysis will be performed in a staged approach. |
| **Rationale for change** | | Biomarker assay analysis is updated. |
| **Section to be changed** | | 7.1 STATISTICAL DESIGN - MODEL |
| **Description of change** | | Update information for primary endpoint at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 7.2 NULL AND ALTERNATIVE HYPOTHESIS |
| **Description of change** | | Update information for primary endpoint at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 7.3 PLANNED ANALYSES |
| **Description of change** | | Update information for primary endpoint at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for |

| | | |
|---|---|---|
| | | slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 7.3.1 Primary endpoint analyses |
| **Description of change** | | Update information for primary endpoint analysis according to method of Reeve. |
| **Rationale for change** | | Primary endpoint analysis is updated. |
| **Section to be changed** | | 7.4 INTERIM ANALYSES |
| **Description of change** | | Update information for DMC, i.e. now fully external DMC. |
| **Rationale for change** | | DMC is changed from a partially external to a fully external DMC. |
| **Section to be changed** | | 7.7 DETERMINATION OF SAMPLE SIZE |
| **Description of change** | | Update information for primary endpoint at Week 12 instead at Week 8. |
| **Rationale for change** | | Primary endpoint is changed to Week 12 instead Week 8, because initial data indicate a potential for slower onset of action for this MoA. Week 12 is now a project standard time-point for primary efficacy measurement. |
| **Section to be changed** | | 9.1 PUBLISHED REFERENCES |
| **Description of change** | | Update references. |
| **Rationale for change** | | One reference is added, one reference is deleted. |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c11253289** **Technical Version Number:4.0**

**Document Name:** clinical-trial-protocol-version-04

**Title:** Proof-of-concept study of BI 655130 add-on treatment in patients with mild-to-moderately active ulcerative colitis during TNF inhibitor therapy.

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Clinical Trial Leader | [redacted] | 05 Mar 2019 15:16 CET |
| Approval-Therapeutic Area [redacted] | | 05 Mar 2019 20:53 CET |
| Approval-Team Member Medicine | | 05 Mar 2019 20:58 CET |
| Approval-Biostatistics | | 06 Mar 2019 04:16 CET |
| Approval-Clinical Pharmacokinetics | | 06 Mar 2019 14:11 CET |
| Verification-Paper Signature Completion | | 13 Mar 2019 07:54 CET |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|